

958
O. 1

Sc
FEBRUARY 1958
VOL. XVII NO. 2

Circulation

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION



*31st Scientific Sessions of the American Heart Association
San Francisco, Calif., from October 24-26, 1958
Deadline for Abstracts June 13, 1958*

GP
101
F50

Published by Grune & Stratton, Inc.

BOSTON UNIVERSITY
COLLEGE OF LIBERAL ARTS
LIBRARY

new
"flavor-timed"
dual-action
coronary vasodilator

Dilcoron

TRADEMARK

ORAL
*for Sustained coronary vasodilation and
protection against anginal attack*

SUBLINGUAL
for Immediate relief from anginal pain

DILCORON contains two highly efficient vasodilators
in a unique core-and-jacket tablet.

Glyceryl trinitrate (nitroglycerin)—0.4 mg. (1/150 grain)
is in the outer jacket—held under the tongue until
the citrus flavor disappears; provides
rapid relief in acute or anticipated attack.

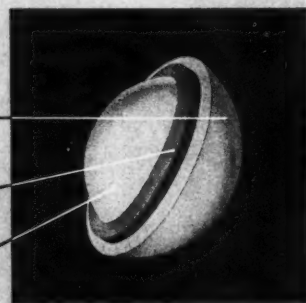
The middle layer of the tablet is
the citrus "flavor-timer."

Pentaerythritol tetranitrate—15 mg. (1/4 grain) is in the
inner core—swallowed for slow enteric
absorption and lasting protection.

*For continuing prophylaxis patients may
swallow the entire Dilcoron tablet.*

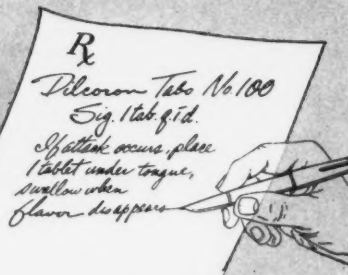
Average prophylactic dose: 1 tablet four times daily.

*Therapeutic dose: 1 tablet held under the tongue
until citrus flavor disappears, then swallowed.*



Bottles of 100.

Winthrop
LABORATORIES
NEW YORK 18, N. Y.



h

Circulation

FEBRUARY 1958
VOL. XVII NO. 2

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Clinical Aspects of Some Diseases of the Small Arteries and Arterioles

ALTHOUGH the smaller blood vessels constitute a large part of the blood vascular system, little interest in or knowledge of their diseases was evident until within recent years.

Even now the state of the small blood vessels in such well-recognized conditions as thromboangiitis obliterans and arteriosclerosis obliterans is largely unknown. Atheromas have been identified in arteries as small as 500 microns in diameter, but further study is necessary to determine how widespread such changes are and how important they may be clinically. Particularly is a study needed in which the histologic findings of atherosclerosis of the small arteries are correlated with the clinical findings in cases in which the larger arteries are not occluded by atheroma and thrombi.

It has been shown only recently that hypertensive changes occur in the arterioles of the skin of patients having essential hypertension that are similar to changes long known to be present in the arterioles of the ocular fundi, the pectoral muscles, the kidneys, and other viscera. That these changes must be of clinical importance in essential hypertension may be surmised from the fact that the skin contains a large part of the smaller blood vessels in the body. Of interest, and

perhaps of significance clinically, is the finding in coarctation of the aorta that hypertensive vascular changes are present and are of equal degree in the skin of the calf and of the arm.

A group of diseases clinically different but having somewhat similar histologic changes in the arterioles includes acrocyanosis, livedoreticularis, chronic pernio, and hypertensive ischemic ulcers of the leg. The predominant changes are varying degrees of arteriolar spasm and arteriolar sclerosis. Except in hypertensive ischemic ulcers, angitis obliterans may involve the capillaries and venules; in cases of livedoreticularis and chronic pernio thickening of the wall and obliteration of the lumen of venules have been observed. The changes are not the result of local inflammation in the skin and subcutaneous tissues because they occur in places where objective evidence of inflammation is absent and ulceration has not developed.

In all of these conditions when spontaneous ulceration occurs, the evolution of the lesion is similar and suggests that arteriolar changes lead to infarction of the skin with the development of an ischemic type of ulcer.

These diseases, like Raynaud's disease, occur predominantly in women. The explanation of this is not clear. Chronic pernio (chronic chilblains) has been considered to occur in women more frequently than in men because women do not protect their legs and

From the Section of Medicine, Mayo Clinic, Rochester, Minn.

ankles adequately from cold. This also may be an explanation of why complications in livedoreticularis, including ulceration in the legs, are seen more often in women than in men. Hypertensive ischemic ulcers of the leg occur mainly in women more than 60 years of age who have had moderate to severe hypertensive vascular disease for many years. One explanation suggested for the predominance in women is that fewer men than women having severe hypertensive vascular disease live to the age of 60.

Most diseases of the smaller blood vessels being considered herein have predominant clinical manifestations in the skin in all cases and chronic ulceration occurs in some cases. When ulceration occurs from infarction, the initial lesion is similar in all of these conditions. Usually the first noticeable abnormality is a painful red plaque on the skin that becomes blue and purpuric within a week or 10 days. A hemorrhagic bleb then develops on the surface of the initial lesion and this breaks down to form the typical superficial ischemic-like ulcer. The surface of the ulcer is usually sensitive and may be very painful, especially when not covered to prevent drying out and exposure to the air.

Acrocyanosis is characterized by persistent coldness and blueness of the extremities, usually of the hands and feet. Most patients are women; they complain of almost constant coldness and bluish coloration of the hands and feet of long duration and more marked during cold weather, although both may be present to a less extent in a warm environment. Blanching such as is seen in Raynaud's disease does not occur. Some swelling and puffiness of the involved parts may occur, particularly in cold weather, and localized regions may become painful or tender. Trophic changes and gangrene do not occur in acrocyanosis and ulceration is rare; if present it usually is the result of some local injury. In almost all cases, acrocyanosis is a relatively innocuous condition. Because of the marked blueness many women are concerned about the uncomely appearance of their extremities and some patients fear

gangrene because of the alarming color change.

Livedoreticularis occurs in women or men of any age. A reddish-blue discoloration with a network-like pattern is characteristic. The legs are usually involved although occasionally the arms and more rarely the body are involved in the peculiar discoloration. The degree of discoloration may vary but some is always present; exposure to cold may intensify the bluish discoloration. Some patients complain of coldness, numbness, aching, and paresthesia of the feet and legs. In most instances the color changes and the discomfort will be the only symptoms the patient observes. However, in about 10 per cent of the cases recurrent ulcerations develop in the skin of the legs.

Livedoreticularis may be symptomatic of other underlying diseases such as systemic lupus erythematosus and periarteritis nodosa, or it may be a primary idiopathic condition. In the symptomatic type livedo is likely to be of a patchy and disseminated nature, whereas in the idiopathic type the reticular pattern is of a diffuse and more or less symmetrical pattern.

In many cases livedoreticularis is not of serious significance and is only important from the cosmetic standpoint. In cases of the symptomatic type, the underlying disease rather than the livedoreticularis will determine the eventual prognosis.

Chronic pernio (chronic chilblains) usually affects women in their thirties and forties who are susceptible to cold and who have large legs with an extra deposit of fat in the subcutaneous tissues. The disease is characterized by recurring erythematous and ulcerating lesions of the lower extremities. In the early years of the disease the lesions always appear at the onset of cold weather and disappear during the summer. They go through a cycle extending over 3 to 6 weeks. Considerable pain may be present, but as ulceration progresses the pain tends to subside. The ulcers heal spontaneously leaving a pigmented scar. After the disease has been present for several years the lesions also may occur during the

summer, particularly if the patient is living where there are intervals of cool days during the warmer summer months. After many recurrences of the lesions, scarring and pigmentation are permanent and may be disfiguring. If the patient is seen during a period when the disease is quiescent or if the disease is long-standing and associated with much inflammation and induration, the diagnosis will be more difficult to establish.

Hypertensive ischemic ulcers occur predominantly in women between 50 and 70 years of age who have had essential hypertension for many years and who have changes in the ocular fundi of chronic hypertensive vascular disease. The ulcers may occur spontaneously but are often initiated by minor injury. They are located most often on the lateral surface of the ankle but occur in some

patients low on the posterior lateral surface of the leg. The ulcer often enlarges by a process of extension of the purpuric hemorrhagic portion into the normal skin around the edges of the ulcer and by subsequent breaking down of the skin. When the ulcer is initiated by injury, these early changes may occur more rapidly and the details of the early processes may not have been noted by the patient. The fully developed ulcers have ranged in size from 1 to 15 cm. in diameter and they are often painful. The patient may come to the physician seeking relief from the severe pain rather than for healing of the ulcerating lesion. In some lesions a thick membranous eschar forms over the ulcer. Almost all lesions heal eventually, but healing may require weeks or even months of treatment.

EDGAR A. HINES, JR.



Medical Eponyms

By ROBERT W. BUCK, M.D.

Raynaud's Disease. "Local Asphyxia and Symmetrical Gangrene of the Extremities" (*De l'asphyxie locale et de la gangrène symétrique des extrémités*) is the title of a thesis submitted for the doctorate in medicine to the faculty of Paris, February 28, 1862 by A. G. Maurice Raynaud (1834-1881), then interne in medicine and surgery. Like more than one other *Thèse de Paris*, this has become a classic. The following quotation is found on page 17:

"I propose to demonstrate the existence of a kind of dry gangrene affecting the extremities, which it is impossible to explain by vascular obliteration; a kind which is characterized particularly by a remarkable tendency to symmetry, in that it always affects similar parts, the two upper or lower extremities, or all four at once; further, in some instances, the nose and the ears, and I shall endeavor to prove that this species of gangrene is caused by a disorder in the innervation of the capillaries . . ."

Pulmonary Heart Disease

With Emphasis on Electrocardiographic Diagnosis

By ROBERT N. ARMEN, M.D., F.A.C.P., MILTON KANTOR, M.D., AND NELSON J. WEISER, M.D.

The diagnosis of cor pulmonale presents considerable difficulty in its earlier stages. Clinical symptoms are not available until the right heart fails and the only reliable sign is right ventricular hypertrophy, which is not easy to demonstrate. The purpose of this investigation is to evaluate electrocardiographic patterns of these patients as a more practical means of diagnosis. Sixty-seven patients with cor pulmonale are included in this study, which endeavors to point out degrees of correlation between various electrocardiographic patterns and clinical factors, such as stages of the disease, its severity, its etiology, and the anatomic changes of the right ventricle. It also evaluates the degrees of specificity of the various patterns encountered in these patients.

THE clinical diagnosis of early right-sided heart disease presents greater difficulties than does that of its counterpart, left-sided heart disease. Once the full-blown pattern of venous engorgement, hepatic congestion, and peripheral edema dominates the clinical picture, no substantial difficulty is encountered in the recognition of right-sided decompensation. At this stage the clinician has practically no need for further laboratory or clinical tests; the physical signs suffice. However, without the clear-cut picture of congestive failure, and especially in borderline stages, or before the advent of early failure, it takes more than the clinical skill of the physician to establish the diagnosis of pulmonary heart disease. This difficulty is often compounded by the presence of the signs and symptoms of the chronic pulmonary disease itself, the etiologic factor responsible for the right-sided heart disease. In a great majority of cases chronic pulmonary disease is characterized by pulmonary emphysema or some form of pulmonary fibrosis. The third major cause of pulmonary heart disease, namely, the various forms of disease in the pulmonary vessels as described by Mack and Snider,¹ has no bearing on the subject of this paper and will not be discussed in detail.

Short of the stage of congestive failure it becomes almost impossible to determine clinically where chronic chest disease ends and right-sided heart disease begins, unless one can demonstrate hypertrophy of the right ventricle,

or abnormal pressure changes in the right side of the heart or in the pulmonary artery by means of cardiac catheterization. This latter means of diagnosis is not generally available except in larger medical centers and is not easily practicable. Therefore, methods of recognition of the early hypertrophy of the right ventricle remain the only practical means of establishing the advent of clinical right-sided heart disease. In the great majority of cases early recognition of right ventricular hypertrophy is uncertain. The only means are by radiologic or fluoroscopic methods and by electrocardiography. Radiographic determination of right ventricular hypertrophy poses considerable difficulty and requires special training and special techniques. Of all the cardiac chambers, enlargement of the right ventricle is the most difficult to demonstrate roentgenologically.² Obvious right ventricular enlargement demonstrable in a posteroanterior or oblique chest film is mostly due to dilatation of the chamber rather than actual hypertrophy alone of the wall of the right ventricle.² By the time dilatation is demonstrable the right side has probably already failed or is in actual failure and, therefore, clinical signs of failure will have been in evidence to establish the diagnosis. In other words, demonstrable enlargement by radiologic means is probably not evidence of early pulmonary heart disease but of heart disease in progress or in failure.

In our opinion chronic chest disease may be in existence for long periods before the advent of right-sided heart disease, just as systemic

From the Medical Service, Veterans Administration Hospital, Wilkes-Barre, Pa.

hypertension may persist for years alone without any evidence of hypertensive heart disease. Actually pulmonary heart disease does not necessarily follow chronic pulmonary disease, just as hypertensive heart disease does not always follow systemic hypertension. It appears to us more logical to disregard the fine differentiation between pulmonary disease and pulmonary heart disease and to consider them together as comprising one "single disease-complex," beginning with pulmonary disease and ending in severe cor pulmonale with cardiac failure. We offer the following simple functional classification of this disease-complex: I, severe pulmonary disease and mild anoxia; II, severe pulmonary disease with anoxia plus right-sided heart disease *without failure*; III, chronic cor pulmonale with cardiac failure. Stages I and II differ very little as far as cardiopulmonary function is concerned, the only difference being the advent of hypertrophy of the right ventricle in stage II. The symptoms manifested in stage II are the symptoms of the primary pulmonary disease, the early hypertrophy of the right ventricle causing no symptoms. We have not been impressed by substernal pain as a symptom in this stage. It is in stage III that one notes severe deterioration of the cardiopulmonary function and clinical evidence of right-sided failure.

During the past 3 years we have been particularly interested in the electrocardiographic diagnosis of pulmonary heart disease as a more practical means of diagnosis. Located as we are in the heart of one of the main hard coal centers of the country, we have had the opportunity of seeing and studying a large number of cases of chronic pulmonary disease, especially anthracosilicosis, emphysema, and the often accompanying pulmonary heart disease. We have developed the study with the following questions in mind: 1. Does clinical cor pulmonale often occur either in the absence of electrocardiographic manifestations or in the presence of manifestations that are not specific for cor pulmonale? 2. If nonspecific electrocardiographic changes are often seen, to what extent may these be taken in conjunction with the known presence of appropriate pulmonary disease to make a reasonable presumptive

diagnosis? 3. Is there any correlation between the type of electrocardiographic changes and the clinical severity of the heart disease?

MATERIALS AND METHODS

The cases of cor pulmonale investigated in this study were obtained from patients currently hospitalized for either their cardiopulmonary disease or for unrelated conditions, and from review of the hospital records of the last 50 consecutive cases whose final discharge diagnoses included cor pulmonale. Each case was thoroughly reviewed, and was accepted for this study only if satisfactory evidence existed to implicate chronic pulmonary disease as the cause for the cardiac disorder. Acceptance was based on either postmortem findings when available, or on clinical grounds in accordance with the criteria of the etiology of heart disease as set forth by the American Heart Association. A total of 67 cases was found to be suitable for the purposes of this study.

Each of the patients selected was suffering from some form of chronic pulmonary disease complicated by the co-existence of heart disease with right ventricular involvement. The latter was indicated by clinical findings such as signs of right-sided heart failure, or by radiologic or electrocardiographic changes consistent with such an interpretation.

The diagnosis of the underlying pulmonary disease was dependent on the history, especially in regard to exposure to industrial dusts, the physical findings, changes in the lungs found on x-ray, pulmonary ventilatory tests, and in one case by pulmonary biopsy. Hematologic studies were also carried out to determine the presence or absence of secondary polycythemia. For the purpose of this paper, this is defined as a red blood count in excess of 6,000,000 or a hematocrit value of more than 55 volumes per cent.

The co-existence of heart disease was easily established when signs of cardiac failure had developed. In addition to the common clinical manifestations of venous engorgement, hepatomegaly with or without ascites, and edema, most cases were also investigated by determinations of the venous pressure, and Decholin and ether circulation times. Radiographic evidence of enlargement of the outflow tract of the right ventricle and dilatation of the pulmonary arteries was also accepted as an indication of right-sided heart disease (fig. 1). In some cases cardiac enlargement without any specific changes in chamber configuration was found and was considered as evidence of heart disease. Cardiac catheterization was not performed on any patient.

During the period of this study 7 patients under investigation were subjected to necropsy examination. Although the normal thickness of the right ventricular wall is stated to be 3 mm., right ventricular hypertrophy was diagnosed only when the

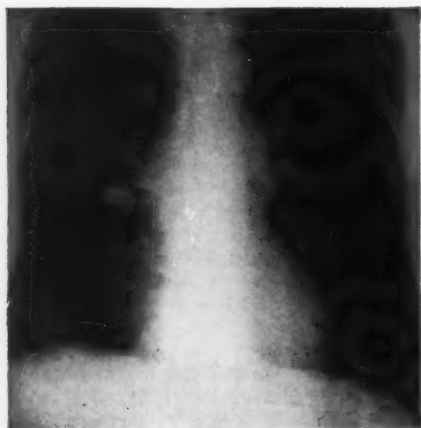


FIG. 1. Posteroanterior chest film showing typical cardiac silhouette, pulmonary fields, and dilated pulmonary arteries of a case of chronic cor pulmonale.

muscle mass measured 5 mm. or more. Because of the difficulty in obtaining entirely accurate measurements of the thickness of the right ventricle, only those were included who died during the period of this study and whose measurements were made personally by one or another of the authors with this investigation in mind. This has necessarily led to a limitation of the number of autopsied cases.

RESULTS

Sex and Age

Consistent with the usual hospital population all patients studied were males. Ages varied from 31 to 87, but with the exception of 2 patients in the early thirties, all were above 50 years of age.

Underlying Chronic Pulmonary Disease

Because of local industrial conditions the majority of the patients studied had been engaged in mining anthracite coal for varying, but usually prolonged periods. Pneumoconiosis due to anthracosilicosis was therefore very common. Some degree of pulmonary emphysema coexisted in almost every instance, and, in many, signs of acute or chronic bronchitis were also found. This combination of lung diseases was present in 41 (61 per cent) cases. Pulmonary emphysema of undetermined etiology was found in 8 (12 per cent), and in an equal number it was secondary to chronic bronchitis. In addition, emphysema was present in 2 cases of

bronchiectasis, and in 1 case each of lung abscess, pulmonary tuberculosis, and chronic diffuse pneumonitis of unknown etiology. The remainder of the patients consisted of 3 of uncomplicated bronchiectasis, 1 of chronic bronchitis, and 1 of pulmonary tuberculosis.

Incidence of Polycythemia

Secondary polycythemia was found in 9 of the cases studied. In each, a diagnosis of pulmonary emphysema had been made with or without one of the associated forms of chronic lung disease mentioned. In addition all of these cases showed signs of heart disease, and 7 were in cardiac failure.

Electrocardiographic Findings

In general, the electrocardiographic patterns in the 67 patients conformed to those already described in the literature, and fell into 1 of 6 groups, as illustrated in figure 2. There was no correlation between the type of tracing and the underlying pulmonary disease. Among the 9 patients with polycythemia, however, 3 fell in group II and 4 in group III.

Group I (fig. 2, col. 1). This group was characterized by tall peaked P waves in leads II, III, and aV_F, and sometimes in the right chest leads, associated with marked clockwise rotation. It included 11 cases (16 per cent). Two of these cases also showed an r/S ratio exceeding $\frac{1}{2}$ in lead V₆. Peaked P waves, however, were often associated with the other electrocardiographic patterns to be described. Also many of the cases of chronic pulmonary disease at this hospital showed the same P-wave changes and clockwise rotation without associated heart disease. The rotation alone may account for the change in the P wave.

Group II (fig. 2, col. 2). Eighteen cases (27 per cent) fell into this group showing the classical pattern of right ventricular hypertrophy with a tall R wave in leads V₁ or V_{4R} with or without a preceding q wave, and followed by an inverted T wave.

Group III (fig. 2, col. 3). Incomplete right bundle-branch block characterized by an rR' with a delayed intrinsicoid deflection but with a QRS duration of less than 0.12 second, and



FIG. 2. Representative electrocardiographic patterns found among 67 cases of chronic cor pulmonale.

TABLE 1.—Association of the Electrocardiographic Pattern in 67 Cases of Chronic Cor Pulmonale with the Severity of the Heart Disease

	Peaked P, clockwise rotation	R in V ₁ or V _{4R}	rR' in V ₁ or V _{4R}	R.B. B.B.	Inverted T over right chest	Miscellaneous
Heart disease with failure....	10	14	12	2	6	7
Heart disease without failure	1	2	4	1	0	0
No other evidence of heart disease.....	0	2	2	2	2	0

an inverted T wave in leads V₁ or V_{4R} occurred in 18 cases (27 per cent). In 3 of the cases right ventricular hypertrophy could be diagnosed by the criteria of Barker^{19, 20} as well as incomplete right bundle-branch block.

Group IV (fig. 2, col. 4). The characteristic electrocardiogram of complete right bundle-branch block was present in 5 cases (7 per cent), and in 3 of these Barker's criteria indicated the co-existence of right ventricular hypertrophy.

Group V (fig. 2, col. 5). T-wave inversions alone, without the previously described R or rR' in V₁ or V_{4R} were present in the right chest leads V_{1, 2, 3} and sometimes V₄ in 8 cases (12 per cent). All these cases showed in addition moderate to marked clockwise rotation with or without peaking of the P waves. The T-wave abnormalities were persistent in 5 patients, one of whom was on maintenance digitalis even prior to the first tracing. They were not permanent in the remaining 3 cases, being present only intermittently in 2, and in the third having disappeared during a 1-year interval between tracings.

Group VI (fig. 2, col. 6). Miscellaneous types of electrocardiograms were obtained from 7 patients (10 per cent). The patterns included 3 normal, 1 with only clockwise rotation, 1 with chronic atrial fibrillation, and 2 with T-wave inversions in the left chest leads.

In all 67 cases of cor pulmonale studied, only 3 cardiac arrhythmias were found. These include chronic atrial fibrillation, paroxysmal atrial fibrillation, and atrial flutter.

Correlation of Electrocardiographic Patterns with Other Signs of Heart Disease

The criteria, aside from the electrocardiogram, accepted in this study as indicative of chronic cor pulmonale have already been described. In short, they are the presence of a pulmonary disease acceptable as an etiologic factor and evidence of congestive failure, or radiologic or postmortem evidence of hypertrophy of the right ventricle. Table 1 indicates the frequency with which the various electrocardiographic patterns were associated with other evidences of heart disease.

This table reveals that of the 11 patients whose electrocardiograms showed only peaked P waves and marked clockwise rotation, 10 (91 per cent) exhibited signs of cardiac failure. The degree of failure as judged by the response to therapy for both the pulmonary and heart disease, was considered mild to moderate, and in no case was it intractable.

Among the 18 cases in group II were 2 cases in which the diagnosis of cor pulmonale was based solely on this characteristic change in the presence of an acceptable etiologic factor. The other 16 all showed other evidences of heart disease, and in 14 (78 per cent) cardiac failure existed. This was mild to moderate in degree in 12 cases, but was intractable in the 2 others. On postmortem examination in 2 cases with mild cardiac failure clinically the right and left ventricles measured 8 and 13 mm. in one instance, and 7 and 12 mm. respectively, in the other. In a third case with no clinical evidence of heart disease the right ventricle was 5 mm. thick.

Among the 18 cases of incomplete right bundle-branch block were 2 in which the diagnosis of heart disease was based on the electrocardiogram and the presence of chronic pulmonary disease. There were 4 cases in which heart disease without cardiac failure was present, and 12 (67 per cent) with definite signs of cardiac failure. In 2 of these the tracing was consistent with the interpretation of co-existent right ventricular hypertrophy. The severity of the cardiac failure was mild to moderate in all 12 cases. Two postmortem examinations were performed on cases with cardiac failure in this group: in them the thickness of the right

ventricular wall was increased to 8 and 10 mm. respectively; both hearts were otherwise normal.

A pattern of complete right bundle-branch block was present in the tracings of 5 patients. Two of these showed no other evidence of heart disease, but in both electrocardiographic changes were also consistent with right ventricular hypertrophy. Three other cases showed evidence of heart disease, and in 2 (40 per cent) cardiac failure was present, moderately severe in one and intractable in the other. The electrocardiogram in the latter instance was also compatible with the presence of right ventricular hypertrophy.

In the 8 cases showing T-wave inversions in the right chest leads and clockwise rotation, 2 had no other evidence of heart disease. The remaining 6 (75 per cent) all were in cardiac failure that was mild to moderate in 5 and intractable in 1. This group of 6 included the 3 cases with inconstant T-wave abnormalities. On postmortem examination in 1 case with changing T waves the right ventricle measured 6 mm., the left 14; the mitral orifice was narrowed to 1 finger and the mitral ring was calcified.

All 7 cases in the group with miscellaneous types of electrocardiograms showed other evidence of heart disease, and all were in cardiac failure. In no case was any etiology other than the chronic pulmonary disease found to account for the cardiac disorder. It is interesting to speculate that the 2 cases with T-wave inversions in the left chest leads might represent examples of left ventricular hypertrophy resulting from abnormal collateral circulation between the bronchial and pulmonary circulations secondary to the pulmonary hypertension. Postmortem examination in 1 patient of this type did reveal thickening of the left ventricular wall to 21 mm., the right to 8 mm., and an increase in the weight of the heart to 650 Gm. The heart was otherwise normal.

The group of the 7 cases that came to autopsy is too small to permit statistically valid conclusions, but there was some correlation between the more significant electrocardiographic changes of right ventricular hypertrophy and its presence anatomically. Similar correlation

was reported by Myers et al.¹⁸ in a much larger series of autopsy material.

DISCUSSION

To simplify the discussion of the findings in the 67 patients investigated, the groups with heart disease and cardiac failure, heart disease without failure, and no other evidence of heart disease, will be examined separately.

In all, there were 51 cases of cor pulmonale that showed varying degrees of heart failure. The electrocardiogram in 10 of these (20 per cent) showed only the clockwise rotation and peaking of the P waves that extensive experience with chronic pulmonary disease and emphysema has demonstrated to be a very common change, even in the absence of heart disease. Like many others, we are inclined to accept this type of tracing as indicative of change in electric axis, and in no way specific for cardiac disease. Nevertheless, these 10 patients had chronic cor pulmonale of sufficient severity to produce heart disease.

There was another group of 7 patients (14 per cent) in whom the electrocardiograms varied from normal to T-wave abnormalities in leads overlying the left ventricle only, but in no instance showing changes even suggestive of right ventricular damage. Each of these patients was in heart failure, attributable, on the basis of presently accepted criteria, to chronic cor pulmonale. The only postmortem examination performed in this group confirmed this; and in the remaining 6 cases clinical investigation failed to suggest any other etiology.

Therefore, in 17 instances (34 per cent) of pulmonary heart disease sufficiently advanced to result in cardiac failure, the electrocardiogram was of no diagnostic assistance. Conversely stated, the absence of electrocardiographic patterns currently assumed to be characteristic of right ventricular disease does not eliminate such disease even in an advanced stage. It should be emphasized at this point that the very method of selection of these patients required the presence of signs of heart disease other than the electrocardiogram. Therefore, the perfect correlation between these nondiagnostic electrocardiograms and other evidence of cardiac involvement resulted from the

method of selection, and should not be assumed to indicate any degree of specificity for the electrocardiographic patterns described.

Among the other patients in cardiac failure, there were 6 (12 per cent) whose tracings showed T-wave inversions over the right leads V_1 through V_3 or V_4 accompanied by clockwise rotation. In this situation, the T-wave abnormalities cannot be accepted as a merely normal variation—the so-called juvenile pattern. In half of these patients, the T-wave abnormalities were inconstant, suggesting that they appeared only during periods of increased right ventricular “strain” secondary to a temporary change in the pulmonary disease. They would then not be indicative of chronic right ventricular damage. The 1 postmortem examination in this type of case, however, does not support this interpretation, since the right ventricle was hypertrophied. In the remaining 5 cases, the possibility of coronary artery disease producing the abnormal T waves cannot be excluded, but the usual supportive evidence for such a diagnosis was lacking in every instance. In this group of 6 patients, the electrocardiogram suggested the possibility of right-sided heart disease but could not be considered diagnostic, despite the fact that again the heart disease had advanced to the point of cardiac failure.

Although the pattern of right bundle-branch block may appear in otherwise normal individuals, its occurrence in the presence of chronic pulmonary disease is very strongly suggestive of cor pulmonale. Whether this change signifies hypertrophy, dilatation, or delayed conduction in the right ventricle will be discussed. Therefore, in the group of 14 patients (27.5 per cent) with cardiac failure, 12 with incomplete and 2 with complete right bundle-branch block, the electrocardiogram was consistent with a diagnosis of right-sided heart disease.

The pathognomonic pattern of right ventricular hypertrophy existed in an additional 14 patients (27.5 per cent) with signs of cardiac failure. The relative infrequency of this pattern again emphasizes that severe cor pulmonale often exists in the absence of classical electrocardiographic changes. However, combining the patients in this group with those showing

complete and incomplete right bundle-branch block presents 55 per cent of the patients with chronic pulmonary disease and cardiac failure in whom the electrocardiogram showed right ventricular involvement.

The number of cases diagnosed as having chronic cor pulmonale without cardiac failure is considerably smaller than those with failure. This, in part, may be due to the recognized difficulty in making the clinical diagnosis in the early stages of right-sided heart disease. In the absence of postmortem examination and, for the purpose of the present investigation, excluding assistance from the electrocardiogram, the “early” diagnosis frequently depends on radiographic changes in heart size and configuration. Accentuation of the pulmonic second sound is indicative of pulmonary hypertension but this may be difficult to evaluate in patients with pulmonary emphysema in whom heart tones are often distant and muffled.

In each of the 8 cases with compensated heart disease the presence of right ventricular enlargement was confirmed by either x-ray or necropsy examination. Table 1 indicates that in 1 of these the electrocardiogram showed only the nondiagnostic peaking of P waves and clockwise rotation; in 5 the complete or incomplete right bundle-branch block consistent with right-sided heart disease in this type of patient; and in 2, the pathognomonic configuration of right ventricular hypertrophy (R in V_1). Therefore, in this group, the electrocardiogram furnished acceptable evidence of right ventricular involvement in 87 per cent of the cases. Among them were 3 cases without clinical or x-ray evidence of heart disease during life, but with definite right ventricular hypertrophy on postmortem examination.

The final group of 8 patients (table 1) includes those in whom a diagnosis of heart disease was based solely on the electrocardiogram. In 2 of these, the tracing was diagnostic, and in the remaining 6 it was consistent with cor pulmonale. Originally, this group also included the 3 patients mentioned above who, on the basis of autopsy findings, were subsequently placed in the category of those with heart disease without failure. It is anticipated that continued observation of the remainder

will eventually disclose other evidence of heart disease besides the electrocardiogram. *Nevertheless, since at present these 8 cases show only electrocardiographic changes, they are not included in the final statistical tabulation in the conclusions.*

Review of the 7 autopsied cases from among the total of 67 patients investigated showed the anatomic presence of right ventricular hypertrophy in each. The electrocardiogram had been diagnostic of right ventricular hypertrophy in 3 and consistent with the diagnosis in 2. It had been merely suggestive in another, and actually misleading in the last, where it had denoted left ventricular disease. Hypertrophy of both ventricles was found at post-mortem examination in this case.

PATHOLOGIC PHYSIOLOGY

The process that terminates in pulmonary hypertension and right-sided failure may begin in several ways: (1) with rupture of interalveolar septa, loss of pulmonary capillary bed, and decreased distensibility of the pulmonary vascular circuit—the usual picture in emphysema; (2) with gradual obliteration of smaller pulmonary vessels by fibrosis secondary to pulmonary granulomata (a broad group including diffuse tuberculosis, sarcoid, silicosis, and berylliosis); (3) with disease in the vessels themselves resulting from such factors as pulmonary hypertension and arteriolar hypertrophy secondary to mitral stenosis of congenital cardiac lesions, multiple pulmonary emboli, carcinomatosis of the lungs, and other less common conditions. Whichever process is primary, the inability of the lung to clear itself of secretions leads to secondary infection and the production of both fibrosis and emphysema. The end result is therefore a composite of at least the first 2 of the above factors. Arterial anoxia results from diffusion defect secondary to fibrosis, as well as from failure to aerate vascularized portions of the lung involved in secondary infection and bronchiolar obstruction. Anoxia has been shown to produce a reflex rise in pulmonary artery pressure, presumably due to pulmonary arteriolar constriction.³ Factors contributing to pulmonary hypertension therefore include actual destruction of pulmonary

vessels, compression of vessels by fibrous tissue, reflex vasoconstriction of the pulmonary arterioles, increased blood viscosity in instances of secondary polycythemia, and increased cardiac output (resulting from hypervolemia, the effect of anoxia on the chemoreceptors, and the stretching of myocardial fibers). Cardiac catheterization in this phase reveals an elevated systolic but normal end-diastolic pressure in a right ventricle, which has not yet failed and still empties completely; an elevated mean pulmonary artery pressure; and a normal "wedge" pressure. In the next phase the right ventricle no longer empties completely; its filling pressure increases; blood is dammed back into the systemic veins and the clinical picture of right heart failure ensues, still (in anoxic, emphysematous patients) with a cardiac output above normal. Prior to the onset of failure, emphysematous patients increase cardiac output at the expense of a disproportionate rise in pulmonary artery pressure and the normal arteriovenous oxygen difference is maintained.⁴ It is not our purpose to present the experimental evidence that has been presented in other papers in support of this concept.^{3, 5-9} Of the factors mentioned, arterial anoxia is the one most consistently found in association with pulmonary hypertension and pulmonary heart disease in cases of "emphysema heart"; it is of course not a factor at all in those patients with heart disease secondary to primary disease of the pulmonary vessels. The central position of anoxia has been emphasized by Cournand,³ Lewis and co-workers,⁵ Harvey et al.⁷ and Gelfand.⁸ Mack and Snider commented that "by the time arterial blood gas abnormalities become demonstrable (in chronic obstructive emphysema), chronic cor pulmonale may be assumed to be present."¹

Patients in failure with cor pulmonale were found by Lewis' group to share many of the characteristics of other forms of heart disease in failure, as well as some basic differences. Similarities included increased arteriovenous oxygen difference and depressed renal function (diminished renal plasma flow and glomerular filtration rate). Lewis thought that oxygen transport per unit time rather than blood flow per unit time is the determinant in fixing the

level of renal blood flow. Patients in failure with cor pulmonale differed from other cardinals with respect to (1) pronounced arterial oxygen unsaturation, probably the most important factor precipitating this form of failure for the reasons noted above; (2) frequent secondary polycythemia; and (3) normal or increased resting cardiac output that, however, fails to increase normally with exercise as it also fails to do in other forms of decompensated heart disease.

We have had 2 patients with cor pulmonale in whom there was left ventricular disease without the presence of any other form of heart disease ordinarily leading to increased work of the left ventricle. In one of the cases the findings were confirmed post mortem. Roosenburg and Deenstra¹⁰ have demonstrated the admixture of oxygenated blood in the smaller pulmonary arteries in patients with chronic lung disease, particularly those with bronchiectasis, indicating an extensive collateral circulation from the bronchial arteries. From the standpoint of the left ventricle this mixing represents an arteriovenous shunt and may be responsible for the left ventricular disease.

Pathophysiology of the Electrocardiographic Pattern

The interpretation of the electrocardiogram in emphysematous patients is subject to error caused by the position of the heart, which is in extreme clockwise rotation. Even V_6 may overlie the right ventricle and it is necessary to take additional leads to the left to obtain the patterns of both ventricles.¹¹ A QS pattern may appear in aV_F in the absence of myocardial infarction because with clockwise rotation the current of septal activation may be at right angles to aV_F , and what would otherwise be an rS (in a horizontal heart) becomes a QS.

With minor points of difference, Wilson, Goldberger, Myers, and others have accepted the following criteria for right ventricular hypertrophy:

1. In the absence of excessive clockwise rotation, leads V_{3R} and V_1 overlie the right ventricle as in the normal heart. With a hypertrophied right ventricular myocardium, the vector toward these leads is increased and is not

dominated, as in the normal heart, by the greater muscle mass of the left ventricle. V_{3R} therefore shows an Rs instead of the normal rS. V_1 may also show an Rs. However, if V_1 lies close to the septum, the later phase of ventricular activation in both ventricles is away from this electrode and an rS may appear despite the presence of a hypertrophied right ventricle. It is therefore important to obtain a V_{7R} or V_{4R} in every case of suspected right ventricular hypertrophy where the diagnosis cannot be made on a standard 12 lead electrocardiogram.¹¹ The tall R (without preceding q) in the right chest leads, often with delayed intrinsicoid deflection, is the only *direct* evidence of right ventricular hypertrophy. Other evidence has been accepted as conclusive, though indirect, and depends on the assumption that extreme clockwise rotation (in the presence of a lesion competent to produce right heart hypertrophy) may be accepted as evidence of right ventricular hypertrophy.¹¹⁻¹³

2. The following evidence of extreme clockwise rotation has been accepted as indirect evidence of right heart hypertrophy under the conditions noted above: (a) A qR pattern in V_1 , or in V_1 and V_2 , is usually considered to indicate that the heart has so rotated on its own long axis as to bring a portion of the left ventricle beneath these electrodes. The qR is therefore the normal recording of the posterior surface of the left ventricle, appearing in an abnormal position. (b) A qR in aV_R where the R is at least 3 times the magnitude of the q, in addition to a deep S wave in all precordial leads such that R/S in V_6 is less than $1/2$.

3. Difficulty is encountered in the diagnosis of right heart hypertrophy in the presence of right bundle-branch block. This may be manifested by: (a) An rSR' pattern in the right precordial leads with a QRS duration of 0.08-0.11 second (experimental evidence to be recorded below indicates that this pattern does not invariably signify incomplete right bundle-branch block). (b) A tall R in the right precordial leads with QRS 0.12 second or more. Goldberger considered the diagnosis of right ventricular hypertrophy not to be possible in the presence of right bundle-branch block.¹³ Braunwald's group accepts the diagnosis of

right ventricular hypertrophy on the basis of the following criteria established by Barker and Valencia:^{14, 19, 20} (a) If the R' is greater than 10 mm. in the presence of incomplete block. (b) If the R' is greater than 15 mm. in the presence of complete block. Braunwald selected 3 groups of patients and measured the time interval between the onset of ventricular activation as indicated by the onset of the QRS on the electrocardiogram and the onset of ventricular contraction as indicated by the first rise in pressure in the catheterized right ventricle. 1. In 15 patients with right heart hypertrophy clinically and electrocardiographically but with no electrocardiographic evidence of conduction defect, this study confirmed the absence of conduction defect. 2. In 6 patients with the electrocardiographic pattern of right bundle-branch block but with no other evidence of heart disease, this study confirmed the presence of right bundle-branch block. 3. In 15 patients similar to the patients in our study, in whom there was clinical reason to suspect right heart hypertrophy and in whom catheterization demonstrated pulmonary hypertension, but in whom the electrocardiogram showed bundle-branch block, two thirds were found to have normal conduction intervals. It would therefore appear that the rSR' and prolonged QRS in these patients was a manifestation of right heart hypertrophy rather than of bundle-branch block. Vectorcardiograms, on the other hand, correctly differentiated the groups and corresponded to the results obtained on catheterization.¹⁵

Other manifestations that may appear in the electrocardiogram in patients with emphysema heart disease have not been accepted as criteria for right ventricular hypertrophy. Peaked P waves may indicate atrial hypertrophy or simply change in the position of the heart.^{1, 16} Inverted T waves in leads subtending the right ventricle indicate "strain" rather than hypertrophy and are often reversible. Finally, superimposition of an acute pneumonic process on a restricted pulmonary bed may produce the electrocardiographic picture of acute cor pulmonale even when embolization has not occurred.

Various groups have found correlation

between pulmonary artery hypertension and the electrocardiographic picture of right ventricular hypertrophy.^{11, 17} In general electrocardiographic changes were not found in the presence of a resting mean pulmonary artery pressure under 30 mm. Hg. In all groups studied a significant number of patients had a pattern generally attributed to complete or incomplete right bundle-branch block rather than hypertrophy. Correlation was also found by Scott et al.¹⁷ between hypoxia and abnormality of the electrocardiographic pattern.

Postmortem studies by Myers and co-workers¹⁸ again emphasized the importance of the pattern of bundle-branch block in these patients. In 40 patients proved post mortem to have right ventricular hypertrophy, 21 had met the classical criteria quoted above for the diagnosis of right ventricular hypertrophy; 12 others met only the electrocardiographic criteria for complete or incomplete right bundle-branch block; 7 met neither of these criteria.

One significant fact emerges from a comparison of our data (table 1) with the data of observers quoted above: In various series, only 50 per cent or fewer of the patients fulfilled the absolute electrocardiographic criteria for right ventricular hypertrophy. The diagnosis of pulmonary heart disease may be made more frequently if the criteria are expanded to include patients with right bundle-branch block (complete or incomplete) and significant T-wave abnormalities over the right chest, in the presence of advanced chronic pulmonary disease. The occasional patient with a combination of chronic pulmonary disease and some other unrelated type of heart disease, may be misdiagnosed on this basis, but the over-all accuracy of the diagnosis in a large series of patients will be greatly improved.

SUMMARY AND CONCLUSIONS

Sixty-seven patients with pulmonary heart disease were investigated in this study. Of these, 59 were found to be suitable for statistical analysis from which the following conclusions are drawn:

In about 30 per cent of the cases of pulmonary heart disease the electrocardiogram alone is not diagnostic; in about 27 per cent the elec-

trocardiogram alone is pathognomonic of right ventricular hypertrophy; in about 42 per cent it is only suggestive, but in the presence of an appropriate pulmonary disease, it becomes strongly suggestive. Clinical pulmonary heart disease of even advanced degree may be present with no more than mild nonspecific electrocardiographic changes and, conversely, pathognomonic electrocardiographic changes may appear in the presence of only mild clinical pulmonary heart disease.

On the basis of postmortem observations in 7 patients, the degree of hypertrophy of the right ventricle correlates well with the electrocardiographic patterns of right ventricular hypertrophy and incomplete right bundle-branch block. But there is no definite correlation between the thickness of the right ventricle and the clinical severity of the pulmonary heart disease.

If complete or incomplete right bundle-branch block, and significant T-wave abnormalities over the right chest leads are considered diagnostic in the presence of an acceptable etiologic factor, then the electrocardiogram might be considered fairly diagnostic in about 69 per cent of cases of pulmonary heart disease. If currently acceptable electrocardiographic criteria are to be chiefly relied upon for the diagnosis of pulmonary heart disease, even in the presence of an acceptable etiologic factor, this diagnosis may be missed in about 31 per cent of cases. For the satisfactory diagnosis of pulmonary heart disease, a combination of clinical, radiologic, and electrocardiographic evidence is necessary in the majority of cases.

ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Miss Mary Burke, Secretary of the Medical Service, and Mr. Andrew Andreeko, Chief of the Medical Illustration Laboratory, who gave freely of their time and skill in helping to prepare this paper.

SUMMARY IN INTERLINGUA

Esseva investigate in le presente studio 67 patientes con morbo cardiac pulmonar. Cinquanta-nove de illes se prestava al analyse statistic, resultante in le sequente conclusiones:

In circa 30 pro cento de casos de morbo

cardiac pulmonar, le electrocardiogramma per se non es diagnostic. In circa 27 pro cento, le electrocardiogramma per se es pathognomonic pro hypertrophia dextero-ventricular. In circa 42 pro cento, le electrocardiogramma pote solmente suggerer le diagnose, sed in le presentia de un pertinente morbo pulmonar, su valor suggestive deveni multo forte. Clinic morbo cardiac pulmonar—mesmo de grados avantiate—pote esser presente in casos exhibiente solmente leve e nonspecific alterationes electrocardiographic, e inversemente, pathognomonic alterationes electrocardiographic pote esser manifeste in le presentia de solmente leve grados de clinic morbo cardiac pulmonar.

A judicar per observationes post morte in 7 patientes, le grado de hypertrophia del ventriculo dextere es ben correlationate con le configuration electrocardiographic typic pro hypertrophia dextero-ventricular e incomplete bloco de branca dextere. Sed il ha nulle correlation del spissitate del ventriculo dextere con le severitate clinic del morbo cardiac pulmonar.

Si, in le presentia de un acceptabile factor etiologic, complete o incomplete bloco de branca dextere e significative anormalitates de unda T in le derivationes dextero-thoracic pote esser considerate como diagnostic, allora le electrocardiogramma es satis definite pro le establimento del diagnose in 69 pro cento del casos de morbo cardiac pulmonar. Si le currentemente acceptate criterios electrocardiographic es usate como base principal pro le diagnose de morbo cardiac pulmonar, allora—mesmo in le presentia de un acceptabile factor etiologic—iste diagnose escappa al detection in circa 31 pro cento del casos. Pro le satisfacente diagnose de morbo cardiac pulmonar, un combination de indices clinic, radiologic, e electrocardiographic es requirite in le majoritate del casos.

REFERENCES

- ¹ MACK, I., AND SNIDER, G. L.: Respiratory insufficiency and chronic cor pulmonale. *Circulation* **13**: 419, 1956.
- ² DOTTER, C. T.: Diagnostic cardiovascular radiology: A changing scene. *Circulation* **14**: 509, 1956.

- ³ Cournand, A.: Some aspects of the pulmonary circulation in normal man and in chronic cardiopulmonary diseases. *Circulation* **2**: 641, 1950.
- ⁴ Hickam, J. B., and Cargill, W. H.: Effects of exercise on cardiac output and pulmonary arterial pressure in normal persons and in patients with cardiovascular disease and pulmonary emphysema. *J. Clin. Invest.* **27**: 10, 1948.
- ⁵ Lewis, C. S., Jr., Samuels, A. J., Daines, M. C., and Hecht, H. H.: Chronic lung disease, polycythemia, and congestive heart failure—cardiorespiratory, vascular, and renal adjustments in cor pulmonale. *Circulation* **6**: 874, 1952.
- ⁶ Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A.: Studies of the pulmonary circulation at rest and during exercise in normal individuals and in patients with chronic pulmonary disease. *Am. J. Physiol.* **152**: 372, 1948.
- ⁷ Harvey, R. M., Ferrer, M. I., Richards, D. W., Jr., and Cournand, A.: Influence of chronic pulmonary disease on the heart and circulation. *Am. J. Med.* **10**: 719, 1951.
- ⁸ Gelfand, M. L.: Effect of chronic pulmonary disease of the heart. *Am. J. Surg.* **89**: 245, 1955.
- ⁹ Fishman, A. P., McClement, J., Himmelstein, A., and Cournand, A.: Effects of acute anoxia on the circulation and respiration in patients with chronic pulmonary disease studied during the "steady state." *J. Clin. Invest.* **31**: 770, 1952.
- ¹⁰ Roosenburg, J. G., and Deenstra, H.: Bronchial-pulmonary vascular shunts in chronic pulmonary effections. *Dis. Chest* **26**: 664, 1954.
- ¹¹ Johnson, J. B., Ferrer, I. M., West, J. R., and Cournand, A.: The relation between electrocardiographic evidence of right ventricular hypertrophy and pulmonary arterial pressure in patients with chronic pulmonary disease. *Circulation* **1**: 536, 1950.
- ¹² Mounsey, J. P. D., Ritzmann, L. W., and Silverstone, N. J.: Cardiographic studies in severe pulmonary emphysema. *Brit. Heart J.* **14**: 442, 1952.
- ¹³ Goldberger, E.: *Unipolar Lead Electrocardiography*. Ed. 3. Philadelphia. Lea and Febiger, 1953.
- ¹⁴ Braunwald, E., Donoso, E., Sapin, S. O., and Grishman, A.: A study of the electrocardiogram and vectrocardiogram in congenital heart disease. Electrocardiographic criteria for ventricular hypertrophy. *Am. Heart J.* **50**: 591, 1955.
- ¹⁵ —, —, —, and —: Right bundle-branch block: Hemodynamic, vectrocardiographic, and electrocardiographic observations. *Circulation* **13**: 866, 1956.
- ¹⁶ Thomas, A. J.: The heart in pneumoconiosis of coal miners. *Brit. Heart J.* **10**: 282, 1948.
- ¹⁷ Scott, R., Kaplan, S., Fowler, N. O., Helm, R. A., Westcott, R. N., Walker, I. C., and Stiles, W. J.: The electrocardiographic pattern of right ventricular hypertrophy in chronic cor pulmonale. *Circulation* **11**: 927, 1955.
- ¹⁸ Myers, G. B., Klein, H. A., and Stoffer, B. E.: The electrocardiographic diagnosis of right ventricular hypertrophy. *Am. Heart J.* **35**: 1, 1948.
- ¹⁹ Barker, J. M., and Valencia, R.: The precordial electrocardiogram in incomplete right bundle branch block. *Am. Heart J.* **38**: 376, 1949.
- ²⁰ —: *The Unipolar Electrocardiogram*. New York, Appleton-Century-Crofts, Inc., 1952, p. 411.

Sarajas, H. S. S., and Cand, M.: Evidence for Heart Damage in Association with Systemic Hypothermia in Dogs. *Am. Heart J.* **51**: 298 (Feb.), 1956.

Twenty-four dogs were subjected to systemic hypothermia. Nine dogs were autopsied at the onset of fatal cardiac irregularities or at the termination of moderate (26 to 27.5 C.) or deep (21 to 22.5 C.) hypothermia of 1 to 4 hours' duration. In all cases the myocardium showed foci of necrotic muscle fibers with an occasional cellular reaction. Fifteen dogs were sacrificed and autopsied 3 days to 3 years after survival of moderate or deep hypothermia of the same duration. In 13 of 15 cases distinct areas of necrosis showing various stages of organization were detected.

RINZLER

Serum Cholesterol in Pentolinium-Treated Arterial Hypertension

By HAROLD H. ORVIS, M.D., IRENE G. TAMAGNA, M.D., AND JOHN M. EVANS, M.D.

Serum lipids were serially determined in 11 patients receiving pentolinium therapy to evaluate changes secondary to blood pressure effects. Substantial reduction in total cholesterol was observed, which in some cases was independent of the hypotensive effect of the drug. Fat absorption, studied in 6 patients, revealed diminished postprandial lipemia in each as compared to placebo determinations. However, few patients showed appreciable weight change during a year of therapy. The evidence suggests that the serum lipid changes secondary to pentolinium administration are due to a qualitative change in fat absorption.

THE association of arterial hypertension and an increased incidence of atherosclerosis has been previously noted.¹⁻³ In studies of atherosclerotic patients assays of the serum lipids have been utilized as an indicator of the status of the disease. These measurements usually include serum cholesterol, phospholipid, and total lipid as well as the determination of the distribution of lipid in the lipoprotein complex by ultracentrifugation, zone electrophoresis, or chemical fractionation. According to Page and associates,⁴ patients with uncomplicated essential hypertension are free of plasma lipid abnormalities. On the other hand, Gofman and associates² have pointed out that the great majority of patients with sustained hypertension have significantly increased serum levels of S_t 10-20 molecules. More marked derangement of the serum lipids might be predicted in a group of patients with long standing severe hypertension presumably with a greater incidence of atherosclerosis. Were such the case, it would be pertinent to determine if measurable changes in the serum lipids are demonstrable during treatment of the hypertension by the currently available hypotensive agents.

From the Department of Medicine, The George Washington University School of Medicine, Washington, D. C.

This work was supported in part by a grant from the Washington Heart Association.

Dr. Orvis was a Fellow in Cardiovascular Disease, the Washington Heart Association 1955-1956.

In this study, serum cholesterol was serially determined in a group of 11 middle-aged patients with severe hypertension during treatment with pentolinium and reserpine and during control periods.

The investigation was extended to include a study of fat absorption when it became evident that a substantial drop in serum cholesterol occurred in many of the patients during treatment. In hypertensive patients receiving hydralazine and hexamethonium (Hyphex), Schroeder⁵ had previously noted a tendency for the serum cholesterol to decrease.

It is the purpose of this paper to report the changes observed in serum lipids incident to pentolinium therapy. Evidence for altered lipid absorption during therapy was obtained in each of the 6 patients so studied. The possible relationship of this finding to the changes in serum lipids during therapy is discussed.

MATERIAL AND METHOD

The patients for this investigation were selected from the Hypertension Clinic, The George Washington University Hospital. Criteria for admission to the study included age 55 or under, sustained diastolic pressure of 110 or greater, and unsuccessful prior treatment with reserpine alone or in combination with hydralazine.

Evaluation prior to therapy included a chest film, an electrocardiogram, the phenolsulfonphthalein test, and determination of the blood urea nitrogen. All of the patients had either electrocardiographic or roentgenologic evidence of left ventricular hypertrophy and 9 of the 11 patients had both. Impaired renal function was indicated

TABLE 1.—Summary of Clinical and Laboratory Data

Patient	Pentolinium dosage(mg./day)	Control pressures*	Treatment pressures†	Serum cholesterol (mg. per cent)			
				Control	3-4 mos.	7-12 mos.	Placebo‡
Men							
B.P.	120	161/128	141/110	354	296	—	—
F.J.	400	197/122	204/137	272	248	—	—
Women							
W.C.	100	268/148	272/135	274	334	280	—
C.G.	180	205/125	165/107	388	288	252	340
L.H.	200	199/113	161/102	292	259	252	282
G.W.	220	239/151	185/118	344	—	223	264
E.H.	240	248/107	178/108	292	202	234	—
M.W.	260	191/133	182/125	403	217	192	287
D.P.	360	205/127	180/114	282	—	385	334
M.P.	500	210/125	202/120	262	172	185	248
L.S.	830	196/133	185/128	221	—	196	—
			Average	307.6	253	249.8	290.8

* Average of all blood pressures obtained in 3-month period prior to therapy.

† Average of all blood pressures (standing) during therapy.

‡ Average of 2 or more determinations.

in all patients by reduced 15-minute excretion of phenolsulfonphthalein, but in none was there elevation of the blood urea nitrogen.

Each of the patients received reserpine, in doses of 0.25 to 0.75 mg. daily, beginning at least 1 month before administration of pentolinium (Ansolysen).⁶ Upon initiation of the latter medication, patients were seen weekly or biweekly until the desired pressure response was obtained. When symptoms of postural hypotension appeared, standing blood pressures were recorded in the clinic every half hour for 3 hours after the midday dose. This procedure was usually satisfactory in establishing the maximum hypotensive effect of the drug. Severe constipation occurred in 6 patients for which 15 mg. of prostigmine bromide or 5 mg. of pilocarpine nitrate was administered daily throughout the study. Patients' diets were not altered and none had been on a low-fat diet. Only 1 subject (E. H.) lost weight during the year of therapy and in this patient there was a complicating illness.

Congestive heart failure was severe (requiring diuretic therapy) in 1 patient (L. S.). Significant fluid retention was not encountered in the other patients, so that we were able to maintain a constant therapeutic regimen during the investigation.

One year after initiation of therapy 6 patients with the least cardiorenal involvement were given a lactose placebo for 6 weeks in place of the pentolinium. Reserpine, parasympathomimetic drugs, and all other medications were continued. Thus,

it was thought that any alteration in serum lipids could be ascribed to withdrawal of the pentolinium.

Blood samples were obtained in the fasting state at the onset of the study and at intervals thereafter. During the placebo period, fasting specimens were obtained biweekly. Serum cholesterol determinations were done in the hospital laboratory by the method of Bloor.⁶ An oral fat-tolerance test was done just prior to and in the third week of the placebo period. The oral fat-tolerance method utilizes changes in serum turbidity after a standard fat meal as a measurement of postprandial lipemia. The test was performed by the method of Waldow and associates.⁷

RESULTS

Pentolinium dosage and average control and treatment blood pressures are presented in table 1. It may be seen that a substantial reduction in average blood pressure was achieved in 6 of the 11 patients. Five of these 6 were in the group given the placebo and in each the blood pressure rose to approximate the pretreatment level.

The serum cholesterol for each individual in relation to the periods of study is given in table 1. It is apparent that the control cholesterol exceeded 250 mg. per cent in 10 of the 11 patients, and, that several patients exhibited a marked drop, the reduction being

*Kindly supplied by Wyeth Laboratories.

most evident in patients with the higher initial cholesterol levels. The average decrease in serum cholesterol was 57.8 mg. per cent, with a range of 24 to 211 mg. per cent. In one subject (D.P.) the cholesterol was higher and in another subject (W.C.) it was unchanged after therapy. It may be pertinent that the latter subject received a relatively small dose of pentolinium.

These findings were further borne out by the results obtained during placebo administration in 6 subjects. Here, it was observed that the cholesterol rose in 5 of the 6. The average level for this group increased from 254.8 to 295.8 mg. per cent. The range of the increase was from 30 to 79 mg. per cent with an average of 48.9 mg. per cent.

The oral fat-tolerance test revealed that the serum turbidity was higher 3 hours after fat ingestion during the placebo period in all 6 patients in comparison with the pentolinium period (table 2). The average optical density at 3 hours was 0.1613 on pentolinium as compared with 0.2405 on placebo. The range of the increase was from 0.0210 to 0.5360 with an average of 0.0792.

DISCUSSION

Coincident with pentolinium administration there was a substantial drop in serum cholesterol in 9 of 11 patients. Schroeder⁵ has reported similar changes in serum cholesterol with the administration of hydralazine and hexamethonium. It is possible that the responsible common factor is the ganglionic-blocking agent. The changes in cholesterol were seen in 3 of our patients in the absence of any lowering of blood pressure. This would seem to indicate that the drop in cholesterol is not due primarily to the decline in arterial blood pressure. Such an inference is further supported by our failure to demonstrate the hypocholesteremic effect in patients rendered hypotensive by reserpine alone or in a patient relieved of hypertension by surgery for coarctation of the aorta.⁸

It is suggested that the observed lipid changes may be due in part to altered lipid absorption, since postprandial lipemia after fat tolerance testing was invariably lower dur-

TABLE 2.—*The Oral Fat-Tolerance Test in 6 Patients*

Patient	Phase of treatment	Fasting	3 hour	5 hour
C.G.	Pentolinium	.0505	.1079	.0655
	Placebo	.0245	.1425	.1024
L.H.	Pentolinium	.0339	.0410	.0505
	Placebo	.0630	.5770	.5450
D.P.	Pentolinium	.0580	.1065	.2041
	Placebo	.0580	.2142	.0969
M.P.	Pentolinium	.0246	.1427	.1024
	Placebo1672	.0862
M.W.	Pentolinium	.0410	.1308
	Placebo	.1458	.1518
G.W.	Pentolinium	.0362	.1163	.1278
	Placebo	.0304	.1905	.0848
Average	Pentolinium	.0407	.1613	.1100
	Placebo	.0443	.2405	.1830

Optical density of sera before and at 3 and 5 hours after ingestion of 40 Gm. of fat. Test performed approximately 1 year after initiation of therapy and in the third week of the placebo period.

ing pentolinium therapy in the 6 patients so studied. The change in lipid absorption would seem to be in the direction of a qualitative alteration rather than reduced absorption, since only 1 of the 11 subjects lost weight during treatment. An additional factor may be the decrease in intestinal motility accompanying ganglionic-blockade therapy. It has been repeatedly shown that the hydrolysis of triglycerides in the small intestine is incomplete during the usual absorptive period.^{9, 10} Increased transit time of food in the small intestine might allow more complete fat digestion prior to absorption. While this could be the mechanism by which pentolinium lowers postprandial lipemia, altered intestinal motility does not readily explain the hypocholesteremic effect. Further study is indicated to clarify this point.

SUMMARY

Fasting serum cholesterol was determined in 11 patients with severe arterial hypertension before and at intervals during treatment

with pentolinium. In 9 of the 11 patients there was a decrease in cholesterol averaging 57.8 mg. per cent for the group, after therapy. These findings were further substantiated in 6 of these patients in that serum cholesterol levels rose during a period of placebo treatment. The lipid changes observed appeared to be independent of the hypotensive effect of pentolinium.

An oral fat-tolerance test revealed lower postprandial lipemia in 6 subjects during pentolinium as compared to placebo treatment. This finding was interpreted as evidence for altered lipid absorption or digestion incident to pentolinium therapy. It is suggested that the alteration is qualitative in nature, since body weight remained stable over a year of treatment in most of the patients.

ADDENDUM

Since the completion of this paper, a similar fall of serum cholesterol has been observed in patients treated with mecamlamine or chlorisondamine; the decrease averaged 26 per cent of control values in a group of 10 patients. It was again noted that the greater effect was in patients with higher initial cholesterol values.

SUMMARIO IN INTERLINGUA

Le cholesterol del sero esseva determinate in stato jejun in 11 patientes con sever hypertension arterial ante e periodicamente durante le tractamento con pentolinium. In 9 del 11 patientes, un reduction de cholesterol esseva notate post le tractamento, amontante a un valor medie pro le gruppo integre de 57,8 pro cento. Iste constatacion esseva corroborate additionalmente in tanto que le nivellos del cholesterol seral montava in 6 del mesme patientes durante un periodo de tractamento a medication fictitie. Le alterationes lipidic observate esseva apparentemente independente del effecto hypotensive de pentolinium.

Un test de tolerantia de grassia oral revelava plus basse nivellos postprandial de lipemia in 6 subjectos durante tractamento a pentolinium que durante tractamento a medication fictitie. Iste constatacion esseva interpretate como prova de un alterate absorption o digestion de lipido in association con le therapia a pentolinium. Es exprimite le opinion que le alteration es de character qualitative, proque le pesos corporee remaneva stabile in le majoritate del patientes in le curso de un anno de therapia.

REFERENCES

1. KATZ, L. N., AND STAMLER, J.: *Experimental Atherosclerosis*. Springfield, Ill., Charles C Thomas, 1953, p. 59.
2. GOFMAN, J. W., JONES, H. B., LINDGREN, F. T., LYON, T. P., ELLIOTT, H. A., AND STRISOWER, B.: Blood lipids and human atherosclerosis. *Circulation* 2: 161, 1950.
3. GOLDSTEIN, F., JENSON, W. K., WALDRON, J. M., AND DUNCAN, G. G.: The relationship between hypertension and coronary occlusion. *Ann. Int. Med.* 44: 446, 1956.
4. PAGE, I., KIRK, E., AND VAN SLYKE, D. D.: Plasma lipids in essential hypertension. *J. Clin. Invest.* 15: 109, 1936.
5. SCHROEDER, H. A.: *Hypertensive Diseases*. Philadelphia, Lea and Febiger, 1953, p. 538.
6. BLOOR, W. R.: The determination of cholesterol in blood. *J. Biol. Chem.* 24: 227, 1916.
7. WALDOW, A., CHAPMAN, J. E., AND EVANS, J. M.: Fat tolerance in subjects with atherosclerosis: heparin effects upon lipemia, lipoproteins, and gamma globulin. *Am. Heart. J.* 47: 568, 1954.
8. ORVIS, H. H., AND EVANS, J. M.: Unpublished data.
9. FRAZIER, A. C., AND SAMMONS, H. G.: The formation of mono- and di-glycerides during the hydrolysis of triglyceride by pancreatic lipase. *Biochem. J.* 39: 122, 1945.
10. MATTSON, F. H., BENEDICT, J. H., MARTIN, J. B., AND BECK, L. W.: Intermediates formed during the digestion of triglycerides. *J. Nutrition* 48: 335, 1952.

Pulmonic Stenosis with Intact Ventricular Septum

Treatment Utilizing Extracorporeal Circulation

By DWIGHT C. McGOON, M.D., AND JOHN W. KIRKLIN, M.D.

Pulmonic stenosis unassociated with a ventricular septal defect of significant size is often a complex abnormality. The stenosis may be valvular, infundibular, or both, and may be associated with an atrial septal defect or even with a small ventricular septal defect. Preoperative studies cannot accurately predict these variations. The surgical approach selected for such patients should permit the correction of each of the cardiac defects encountered. That this can be accomplished by means of extracorporeal circulation and open cardiomy is demonstrated by the presented series of 10 cases without operative mortality.

PULMONIC stenosis may be valvular, subvalvular, or both valvular and subvalvular. Although often occurring as an isolated defect, it may be associated with certain other intracardiac abnormalities. These several possible combinations of defects have resulted in difficulties of classification and in discrepancies of terminology.

DEFINITIONS

To a considerable degree, matters of classification and terminology are arbitrary, but it is important that all terms be clearly defined. The distinction between valvular pulmonic stenosis and subvalvular or infundibular pulmonic stenosis is now generally recognized.

In the tetralogy of Fallot, there is, in addition to pulmonic stenosis, a ventricular septal defect of a size that approximates that of the aortic orifice. At the opposite extreme is the heart in which there is pulmonic stenosis and an intact ventricular septum. Difficulty in classification is posed by the heart with pulmonic stenosis, but with a very small ventricular septal defect. Since patients with this combination seen at the Mayo Clinic have clinically resembled those patients with pulmonic stenosis and intact ventricular septum, it appears wise from a practical standpoint to classify these in the same group. They might be designated as having "pulmonic stenosis with essentially intact ventricular septum." Efforts to distinguish these hearts from those

with so-called "tetralogy of Fallot" on the basis of the presence or absence of dextroposition of the aorta, or the nature of the pulmonic stenosis, have not been satisfactory.

The present study deals with pulmonic stenosis either with an intact ventricular septum or with a very small ventricular septal defect. In this type of cardiac deformity there also may or may not be an interatrial communication that permits usually a right-to-left shunt, and less commonly a left-to-right shunt.^{1,2}

CHARACTERISTICS OF THE PULMONIC STENOSIS

It is believed of primary importance to re-emphasize that infundibular stenosis is frequently encountered in those patients having pulmonic stenosis with an intact ventricular septum. Previously, several reports³⁻⁶ have been made of patients having isolated valvular pulmonic stenosis and an intact ventricular septum, with the apparent exclusion of any such patients also having infundibular pulmonic stenosis. The misconception might thereby arise that in all such patients the pulmonic stenosis is exclusively valvular. On the other hand, even the nonsurgical literature reports an incidence of infundibular stenosis as high as 14⁷ to 25 per cent⁸ in these patients, either alone or in combination with valvular stenosis; in certain surgical series where infundibular stenosis has been looked for carefully, an equally high or higher incidence has been found.^{9, 10} Infundibular stenosis occurred with similar frequency in our total experience with the indirect technic of pulmonic valvotomy.

Thirty-two patients classified as having

From the Mayo Clinic and the Mayo Foundation, Rochester, Minn. The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

TABLE 1.—Incidence of Association of Valvular and Infundibular Stenosis in Pulmonic Stenosis with Presumably Intact Ventricular Septum

Age (years)	Valvular stenosis unassociated with significant infundibular stenosis		Combined valvular and significant infundibular stenosis		Total
	Pa-tients	Per cent of total	Pa-tients	Per cent of total	
Less than 15...	14	78	4	22	18
15 or more....	5	36	9	64	14
All ages.....	19	59	13	41	32

pulmonic stenosis with intact ventricular septum have undergone operation at the Mayo Clinic by the closed technic with transventricular approach to the pulmonic valve. The first 12 have been previously reported in detail.⁹ In 13 of the 32 patients (41 per cent) the pulmonic stenosis was combined with significant infundibular stenosis (table 1), and in 5 of these 13 the infundibular stenosis was severe.* Numerous additional authors have recognized the occurrence of infundibular stenosis in this type of cardiac anomaly.¹¹⁻¹⁸ It should be realized, however, that only pressure determinations before and after pulmonic valvotomy can accurately detect certain associated infundibular stenoses that might otherwise have been overlooked.

Recently a distinction has been recognized between the infundibular stenosis as found in this group having an intact ventricular septum and the infundibular stenosis associated with a large ventricular septal defect. The possibility has been suggested^{12, 18} that muscular hypertrophy of the right ventricular outflow tract, secondary to pulmonic valvular stenosis, may cause obstruction from its own bulkiness and sphincterlike action, and thus perpetuate a vicious cycle of stenosis, hypertrophy, and more stenosis.

Furthermore, it is of interest that infundibular stenosis in association with valvular pulmonic stenosis apparently occurs with greater frequency in adults than in children,

* Infundibular stenosis is considered significant when the low right ventricular systolic pressure is more than 20 mm. Hg greater than that in the infundibular zone, and severe when it is more than 40 mm. Hg greater.

suggesting that time is required for the development of obstructing muscular hypertrophy of the infundibulum. This is again demonstrated by our series of patients operated on by the closed approach. As shown in table 1, the incidence of significant infundibular stenosis in addition to valvular stenosis increased from 22 per cent in children to 64 per cent in patients 15 years of age and older. Yet the infundibular stenosis encountered in this group of patients cannot be entirely the result of secondary muscular hypertrophy, for it may occur, as in cases 2 and 6 in table 2, in hearts with normal pulmonary valves.

FEASIBILITY OF COMPLETE SURGICAL CORRECTION

Pulmonic stenosis with essentially intact ventricular septum may thus consist of valvular or of infundibular stenosis, or of both, and may be associated with an atrial septal defect, or a small ventricular septal defect, or both. If it can be demonstrated that all these abnormalities are correctable with little or no additional operative risk, obviously this should be preferable to only partial correction.

A total of 10 patients with this condition have been operated on by means of extracorporeal circulation and open cardiomy at the Mayo Clinic prior to January 1, 1957. A summary of the essential data in these cases is presented in table 2.

All patients were free of peripheral edema at the time of operation. All had a loud coarse systolic murmur and a palpable thrill in the pulmonic area. The second pulmonic sound was obscure or absent in all except case 8. The electrocardiograms and roentgenograms showed alterations commensurate with the anatomic and hemodynamic findings.

It should be noted from table 2 that the preoperative right ventricular systolic pressures ranged from 83 to 227 mm. Hg and that the systolic pressure gradient between the right ventricle and the pulmonary artery ranged from 52 to 210 mm. Hg. At operation the pulmonic stenosis was found to be exclusively valvular in only 2 patients and entirely infundibular in 3 patients; both infundibular and valvular stenosis were found in the remaining 5 patients.

TABLE 2.—Data in Ten Operative Cases

Case, sex, age (years)	N.Y. heart class	Cyanosis	Preoperative heart catheterization				Operative diagnosis	Atrialotomy for repair of atrial septal defect	Pulmonary arteriotomy for atrial valvulopathy	Ventriculotomy for resection of infundibular stenosis	Postcorrection systolic pressure at operation (mm. Hg)		Result
			Rt. ventricle, systolic pressure (mm. Hg)	Pulmonary artery, systolic pressure (mm. Hg)	Rt.-to-left shunt, per cent (O ₂ saturation data)	Peripheral arterial O ₂ saturation, per cent					RV	PA	
1, F, 44	III D	+	208	12	31	84	Valvular and infundibular stenosis; probe-patent foramen ovale	0	+	+	60	25	Died 3 mo. p.o. after saddle embolus
2, F, 11	III D	+	160	19	—	92	Infundibular stenosis, probe-patent foramen ovale	0	0	+	20	20	Excellent
3, F, 33	III D	+	210	13	25	85	Valvular and infundibular stenosis; 8-mm. defect in foramen ovale	+	0	+	50	20	Excellent
4, M, 10	II B	0	98	34	0*	98	Infundibular stenosis; bi- cuspid nonobstructing pulmonic valve; ventric- ular septal defect 5 mm.	0	0	+	49	24	Excellent
5, F, 8	III C	+	175	—	—	92	Valvular and infundibular stenosis; atrial septal de- fect 8 mm. and 2 addi- tional fenestrations	+	+	+	30	14	Excellent
6, F, 39	II C	0	153	—	—	95.5	Infundibular stenosis; ven- tricular septal defect 4 mm.	0	0	+	22	—	Excellent
7, M, 40	II C	+	97	18	6	94	Valvular and infundibular stenosis; 2 small openings in foramen ovale	+	+	+	—	—	Excellent
8, F, 4	I B	0	83	31	0*	99	Atrial septal defect, 30 × 15 mm.; valvular pul- monic stenosis	+	+	0	25	20	Excellent
9, M, 14	III C	+	121	—	47	96.5	Valvular and infundibular stenosis; atrial septal de- fect 10 mm. and 3 or 4 fenestrations	+	+	+†	35	25	Excellent
10, M, 38	IV D	0	227	17	0	93.4	Valvular-pulmonic stenosis	0	+	0	45	35	Excellent

* These 2 patients had significant left-to-right shunts.

† An Ivalon diamond-shaped prosthesis in outflow tract incision.

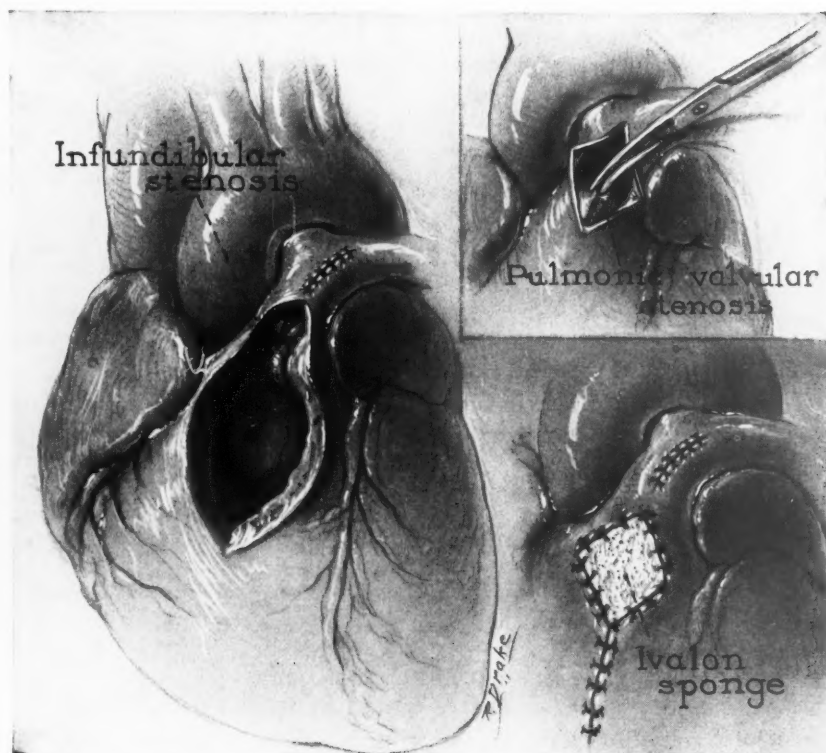


FIG. 1. The stenotic pulmonic valve is being incised along the vestigial commissure through a pulmonary arteriotomy (inset). High infundibular stenosis and hypoplasia of the outflow tract of the right ventricle were also present, and these were not adequately relieved by resection of infundibular tissue. Therefore a diamond-shaped piece of compressed Ivalon was inserted as illustrated to eliminate the narrowing of the outflow tract.

Small atrial septal defects, located in the foramen ovale, were present in 3 instances, and each was closed through an open right atriotomy. Two patients had a relatively large atrial septal defect, each of which was similarly closed. In addition, 2 instances of a probe-patent but valvular-competent foramen ovale were noted but were not treated.

Very small ventricular septal defects were present in 2 hearts; in both of these the pulmonic stenosis was infundibular, without valvular obstruction. In case 4, the defect lay just inferior to the infundibular stenosis, and in case 6, just superior to it. Both ventricular septal defects were closed through the open right ventriculotomy.

Each of the 7 stenotic pulmonic valves could be precisely opened under direct vision. In 6

cases the valve was approached through an incision in the main pulmonary artery, as shown in the inset of figure 1. The 1 remaining stenotic valve was incised through the right ventriculotomy.

Resection of the infundibular stenosis under direct vision was performed in each case through a right ventriculotomy. Of extreme interest is the fact that during 2 of the 5 operations (cases 1 and 5) on hearts with associated infundibular and valvular stenosis, the presence of the infundibular stenosis was not suspected during the pulmonic valvotomy through the pulmonary artery. Only after normal blood flow through the heart and lungs had been resumed, and extracorporeal circulation had been discontinued, did measurements of right ventricular and pulmonary arterial pressures

demonstrate infundibular stenosis. It was then necessary to re-establish extracorporeal circulation, open the right ventricle, and resect the infundibular stenosis.

In the ninth patient of this series, the infundibular stenosis was subvalvular and could not be relieved by simple excision of redundant muscular and endocardial tissues, and thus resembled the condition in a number of patients previously encountered in our tetralogy series. This patient was treated by a technic¹⁹ that has been employed in certain patients with tetralogy. Even after excision of all possible redundant infundibular tissues, it became obvious that closure of the infundibular portion of the right ventricular incision would result in residual infundibular stenosis. Consequently this portion of the incision was not closed, but rather hemostasis and continuity of the right ventricular wall were accomplished by the insertion of a diamond-shaped piece of compressed Ivalon. This was sutured carefully about its periphery to the epicardial edge of the ventriculotomy wound, as depicted in figure 1. The technic is somewhat analogous to the pyloromyotomy that is employed in the treatment of hypertrophic pyloric stenosis.

Especially to be noted from table 2 are the pressure measurements recorded at operation following relief of the pulmonic stenosis. The systolic pressure gradients between the right ventricle and the pulmonary artery range from 0 to 35 mm. Hg, with an average of 16 mm. Hg.

There were no operative deaths in the series, and the only serious postoperative complication occurred in the first patient. She died 3 months after cardiac operation, shortly after the removal of an acute saddle embolus of the aorta. Just prior to this event she had made rapid progress following a stormy convalescence.

The remaining 9 patients have had excellent results. They were dismissed from the hospital 10 to 18 days after operation. Only 1 diastolic murmur (limited to early diastole) has been detected postoperatively, and indeed, 2 cases (cases 2 and 6) have shown complete absence of all murmurs. The remainder show systolic pulmonic murmurs. The electrocardiographic

pattern of right bundle-branch block, complete or incomplete, was consistently encountered postoperatively.

TECHNIC OF OPERATION

The surgical technic employed in these patients requires little description beyond that previously presented. The basic principles and technics for whole-body perfusion utilized for these operations have been described.^{20, 21}

Atrial septal defects are closed through a right atriotomy. The stenotic pulmonic valve is repaired through an incision in the main pulmonary artery by radial incisions made with scissors to produce a tricuspid or bicuspid valve (fig. 1).

Ordinarily, infundibular stenosis may be relieved simply by excision of redundant infundibular muscle and thickened endocardium with the scalpel and scissors. As in 1 instance in the series reported here, however, the insertion of an Ivalon prosthesis to relieve a high infundibular stenosis may be required.

There are, of course, many details that require attention in the operative and postoperative management of these patients, perhaps the most important of which are accurate blood replacement and frugality in the administration of fluids.

DISCUSSION

Three general types of surgical technic for the relief of pulmonic stenosis with intact ventricular septum are currently applicable, namely, an indirect approach, a direct approach with use of hypothermia, and a direct approach with use of extracorporeal circulation. The first utilizes an indirect or blind access to the valvular stenosis, either by way of the right ventricle as introduced by Brock²² and by Sellors,²³ or by way of the pulmonary artery as introduced by Pettersson.²⁴ Cutting and dilating instruments are passed through the stenotic pulmonic valve. The low mortality rate of this procedure and the excellent postoperative subjective improvement are gratifying.

However, objective postoperative studies have shown less than the desired reduction of the pressure gradient between right ventricle and pulmonary artery in the majority of these cases.^{3-5, 9, 25-27} The prognostic significance of this result will not be fully appreciated until prolonged follow-up studies are available. Furthermore, associated anomalies, including atrial septal defect, ventricular septal defect,

and infundibular stenosis, cannot be readily repaired when this technic is used.

In our experience with this indirect procedure it has been particularly those patients exhibiting cyanosis preoperatively who have had the less satisfactory results. A mortality rate of 36 per cent of the 14 patients in the cyanotic group is compared to 0 per cent of the 18 in the acyanotic group. Even significant reduction of right ventricular pressures, which occurred in 7 of the 9 surviving cyanotic patients, resulted in a satisfactory relief* of cyanosis in only 3. For these reasons we have now abandoned the indirect approach to the pulmonary valve in patients who are cyanotic.

Swan and his associates^{6, 28} have presented their experience in which hypothermia and circulatory arrest are instituted to enable direct-vision valvuloplasty through a pulmonary arteriotomy. In their reported series, a "total cure" was accomplished in 11 of the 12 patients—an excellent record.

An argument might be made against the use of hypothermia in the treatment of pulmonic stenosis, however, because satisfactory infundibular resection by this technic would seem both difficult and dangerous. Since, as shown, infundibular stenosis is frequently encountered in pulmonic stenosis with an intact ventricular septum and often cannot be accurately predicted preoperatively, one must accept the possibility of incomplete relief of pulmonic stenosis in this sizable group if the technic employing hypothermia is used.

It is true that in our experience and that of others, in some patients infundibular stenosis that was demonstrated at cardiac catheterization during the first few weeks after valvotomy regressed completely in the 12 to 18 months after operation. Nonetheless, there is evidence that severe residual infundibular stenosis adds to the hazards of the postoperative period, and it is on this account that one may have some concern as to the routine choice of hypothermia for the management of these cases.

The third approach to the surgical treatment of these patients utilizes extracorporeal circula-

tion and any or all of ventriculotomy, atriotomy, and pulmonary arteriotomy, thus providing optimal conditions for restoration of normal anatomy.

For cyanosed patients with pulmonic stenosis and intact ventricular septum, it is our practice to use extracorporeal circulation, thus permitting closure of the atrial septal defect and repair of the pulmonic stenosis. Likewise, whenever the presence of infundibular stenosis is suspected from catheterization data or because of the empirical observation of its frequency of occurrence after childhood, extracorporeal circulation with open cardiectomy is selected. Only when valvular pulmonic stenosis is strongly suspected of being a truly isolated lesion is there some room for debate, in our opinion, in choosing between extracorporeal circulation, hypothermia, or a closed technic. Further experience is necessary before final conclusions can be made on these matters.

SUMMARY

Pulmonic stenosis with presumably intact ventricular septum is frequently a complex abnormality, for the stenosis may be valvular or infundibular and may be associated with an atrial septal defect or even with a small ventricular septal defect.

The feasibility of complete correction of these several possible associated cardiac abnormalities, by means of extracorporeal circulation and open cardiectomy, is exemplified by the presented series of 10 cases without operative mortality, in 9 of which an excellent result was obtained. One patient died 3 months after operation.

SUMMARIO IN INTERLINGUA

Stenose pulmonic con septo ventricular apparentemente intacte es frequentemente un anormalitate complexe, proque le stenose pote esser valvular o infundibular e pote esser associate con un defecto atrio-septal o mesmo con un parve defecto ventriculo-septal.

Le practicabilitate del correction complete de iste varie anormalitates cardiac de occurrentia associate possibile, effectuate per medio de circulation extracorporee e cardiectomia aperte, es exemplificate per le hic

* A residual right-to-left shunt of less than 15 per cent, or a resting arterial oxygen saturation of more than 92 per cent.

presentate serie de 10 casos sin mortalitate operatori. In 9 casos le resultado esseva eccellente. Un patiente moriva 3 menses post le operation.

REFERENCES

- ¹ BROADBENT, J. C., WOOD, E. H., AND BURCHELL, H. B.: Left-to-right intracardiac shunts in the presence of pulmonary stenosis. *Proc. Staff Meet., Mayo Clin.* **28**: 101, 1953.
- ² CALLAHAN, J. A., BRANDENBURG, R. O., AND SWAN, H. J. C.: Pulmonary stenosis and ventricular septal defect with arteriovenous shunts: A clinical and hemodynamic study of eleven patients. *Circulation* **12**: 994, 1955.
- ³ BLOUNT, S. G., JR., MCCORD, M. C., MUELLER, H., AND SWAN, H.: Isolated valvular pulmonic stenosis: Clinical and physiologic response to open valvuloplasty. *Circulation* **10**: 161, 1954.
- ⁴ HOSIER, D. M., PITTS, J. L., AND TAUSSIG, H. B.: Results of valvulotomy for valvular pulmonary stenosis with intact ventricular septum: Analysis of 69 patients. *Circulation* **14**: 9, 1956.
- ⁵ LILLEHEI, C. W., WINCHELL, P., ADAMS, P., BARANOFFSKY, I., ADAMS, F., AND VARCO, R. L.: Pulmonary valvular stenosis with intact ventricular septum: Results of the Brock type valvulotomy. *Am. J. Med.* **20**: 756, 1956.
- ⁶ SWAN, H., CLEVELAND, H. C., MUELLER, H., AND BLOUNT, S. G., JR.: Pulmonic valvular stenosis: Results and technique of open valvuloplasty. *J. Thoracic Surg.* **28**: 504, 1954.
- ⁷ SELZER, A., CARNES, W. H., NOBLE, C. A., JR., HIGGINS, W. H., JR., AND HOLMES, R. O.: The syndrome of pulmonary stenosis with patent foramen ovale. *Am. J. Med.* **6**: 3, 1949.
- ⁸ GREENE, D. G., BALDWIN, E. DE F., BALDWIN, J. S., HIMMELSTEIN, A., ROH, C. E., AND COURNAND, A.: Pure congenital pulmonary stenosis and idiopathic congenital dilatation of the pulmonary artery. *Am. J. Med.* **6**: 24, 1949.
- ⁹ KIRKLIN, J. W., CONNOLLY, D. C., ELLIS, F. H., JR., BURCHELL, H. B., EDWARDS, J. E., AND WOOD, E. H.: Problems in the diagnosis and surgical treatment of pulmonic stenosis with intact ventricular septum. *Circulation* **8**: 849, 1953.
- ¹⁰ GLOVER, R. P., O'NEILL, T. J. E., GONTIGO, H., McAULIFFE, T. C., AND WELLS, C. R. E.: The surgery of infundibular pulmonic stenosis with intact ventricular septum (a type of "pure" pulmonic stenosis). *J. Thoracic Surg.* **28**: 481, 1954.
- ¹¹ THEILEN, E. O., AND JANUARY, L. E.: Stenosis of the pulmonary conus without associated defects: A case report. *J. Iowa M. Soc.* **41**: 88, 1951.
- ¹² RODBARD, S., AND SHAFFER, A. B.: Muscular contraction in the infundibular region as a mechanism of pulmonic stenosis in man. *Am. Heart J.* **51**: 885, 1956.
- ¹³ EMSLIE-SMITH, D., LOWE, K. G., AND HILL, I. G. W.: The intracardiac electrogram as an aid in the localization of pulmonary stenosis. *Brit. Heart J.* **18**: 29, 1956.
- ¹⁴ EKSTRÖM, G., LUNDBERG, A., AND MÖLLER, T.: Postoperative studies of pulmonary stenosis without aortic overriding. *Acta paediat.* **45**: 32, 1956.
- ¹⁵ DRYERRE, H. W., AND WALMSLEY, R.: Stenosis at the lower bulbar orifice of the infundibulum. *Brit. Heart J.* **1**: 325, 1939.
- ¹⁶ COELHO, E., AND DE OLIVEIRA, A.: Stenosis of the pulmonary infundibulum with intact ventricular septum: A case report with anatomic confirmation. *Clin. contemp.* **5**: 57, 1951.
- ¹⁷ CAMPBELL, M.: Simple pulmonary stenosis: Pulmonary valvular stenosis with a closed ventricular septum. *Brit. Heart J.* **16**: 273, 1954.
- ¹⁸ BROCK, R.: Control mechanisms in the outflow tract of the right ventricle in health and disease. *Guy's Hosp. Rep.* **104**: 356, 1955.
- ¹⁹ WARDEN, H. E., DEWALL, R. A., COHEN, M., VARCO, R. L., AND LILLEHEI, C. W.: A surgical-pathologic classification for isolated ventricular septal defects and for those in Fallot's tetralogy: Based on observations made on 120 patients during repair under direct vision. *J. Thoracic Surg.* **33**: 21, 1957.
- ²⁰ JONES, R. E., DONALD, D. E., SWAN, H. J. C., HARSHBARGER, H. G., KIRKLIN, J. W., AND WOOD, E. H.: Apparatus of the Gibbon type for mechanical bypass of the heart and lungs. *Proc. Staff Meet., Mayo Clin.* **30**: 105, 1955.
- ²¹ HARSHBARGER, H. G., KIRKLIN, J. W., AND DONALD, D. E.: Studies in extracorporeal circulation: IV. Surgical techniques. *Surg., Gynec. & Obst.* In press.
- ²² BROCK, R. C.: Pulmonary valvulotomy for the relief of congenital pulmonary stenosis: Report of three cases. *Brit. M. J.* **1**: 1121, 1948.
- ²³ SELLORS, T. H.: Surgery of pulmonary stenosis: A case in which the pulmonary valve was successfully divided. *Lancet* **1**: 988, 1948.
- ²⁴ PETERSSON, G.: A simple method of pulmonic valvotomy in valvular pulmonary stenosis. *Acta chir. scandinav.* **107**: 531, 1954.
- ²⁵ BROCK, R.: Direct operations in the treatment of pulmonary stenosis. *Brit. M. Bull.* **11**: 189, 1955.
- ²⁶ LURIE, P. R., AND SHUMACKER, H. B., JR.: Hemodynamic effects of valvulotomy in pulmonic stenosis. *Circulation* **8**: 345, 1953.
- ²⁷ SILVERMAN, B. K., NADAS, A. S., WITTENBERG, M. H., GOODALE, W. T., AND GROSS, R. E.: Pulmonic stenosis with intact ventricular septum: Correlation of clinical and physiologic data, with review of operative results. *Am. J. Med.* **20**: 53, 1956.
- ²⁸ SWAN, H., VIRTUE, R. W., BLOUNT, S. G., JR., AND KIRCHER, L. T., JR.: Hypothermia in surgery: Analysis of 100 clinical cases. *Ann. Surg.* **142**: 282, 1955.

Intravenous Protein-Free Pyrogen

A Powerful Fibrinolytic Agent in Man

By KURT N. VON KAULLA, M.D.

Administration of a variety of nonfibrinolytic, nonenzymatic substances induces fibrinolysis in man. The most potent materials of this type known at present are purified protein-free pyrogens. Their action after intravenous injection on the human fibrinolytic system, on some of its components, and on the clotting system of 67 individuals has been studied. The possible therapeutic implications are discussed of the marked fibrinolysis.

THE obvious therapeutic value of activation of fibrin-dissolving potentialities of the circulating human blood in thromboembolic disorders, has stimulated many efforts to achieve this goal. These attempts may be classified under 2 general headings: injection of proteolytic enzymes, and the activation of plasminogen in the body itself. The most important drugs known to produce fibrinolysis in human beings and some of their characteristics are summarized in table 1.

The induction of fibrinolysis in the human body with nonenzymatic material can be produced (table 1) in many ways. In the majority of cases, however, the fibrinolytic reactions are either weak or too irregular to be of therapeutic value.

The observation of Eichenberger,¹³ that Westphal's¹⁴ highly purified protein-free pyrogen produces fibrinolysis in man after intravenous injection, was therefore of special interest. We have confirmed these preliminary findings and have extended these observations considerably with more comprehensive studies. The protein-free pyrogens described below, as far as we have been able to determine, are the most potent nonenzymatic fibrinolysis-inducing agents known at present.

From the Department of Medicine, University of Colorado School of Medicine and the Belle Bonfils Memorial Blood Bank, Denver, Colo.

This work was done during the tenure of Research Fellowship of the American Heart Association. Supported by grants-in-aid from the American Heart Association and the Wander Foundation, Chicago, Ill.

In this paper the pyrogenic materials used and their action in man are described with special emphasis on fibrinolysis. A short summary of some of our experiments has previously been given.¹⁵

MATERIAL AND METHODS

Pyrogens. Two pyrogens were used. 1. Preparation 1064 is derived from *Salmonella abortus equi* and has a molecular weight of about 1 to 2,000,000. It consists of 30 to 40 per cent phospholipids, 6 to 10 per cent esters of phosphoric acid, and 55 to 60 per cent different sugars and is free from proteins and amino acids. 2. Preparation 1083 is derived from *Escherichia coli* and has been acetylated. Its analysis reveals a composition of 50 per cent sugars, 25 to 27 per cent acetyl groups, 18 per cent phospholipid components, and 5 per cent esters of phosphoric acid. Its molecular weight is about 1,000,000. Both preparations are water soluble. They were donated as sterilized solutions in ampules by the Wander Company, Chicago. Preparation 1064 had 1 µg. per ml., preparation 1083 had 100 µg. per ml.

To study the nature of the fibrinolytic reaction induced by these pyrogens the following methods were used:

Fibrinolysis. (a) A continuous recording (coagulogram) of fibrin formation and dissolution of recalcified citrated plasma¹⁶ was made. One part of 3.8 per cent sodium citrate to 4 parts of blood was used, spun for 5 minutes at 1,500 g and recalcified with one tenth volume of 0.5 molar calcium chloride. (b) The dissolution time was measured of a plasma clot from 0.3 ml. of undiluted plasma plus 0.01 ml. of thrombin 200 U per ml., and (c) also the dissolution time of a thrombin clot from plasma diluted 1:19 with buffered saline. (d) Measurement of the dissolution time of a clot obtained from euglobulins: (precipitate was formed after carbon dioxide saturation of plasma diluted 1:19 with distilled water); euglob-

TABLE 1.—*Summary of the Most Important Drugs Producing Fibrinolysis In Man*

Drug	Intensity of action	Duration of action	Active in test tube	Mechanism of action	Remarks	Reference no.
Trypsin i.v.	weak	short	yes	direct digestion of fibrin. Activation of plasminogen.	Effect is uncertain	1 2
Plasmin i.v.	strong	during infusion	yes	direct digestion of fibrin		3
Streptokinase i.v.	strong	during infusion	yes	activation of proactivator		4
Acetylcholin i.v.	strong	few minutes	no	?	effective near shock level	5
Epinephrine s.c.	weak	fraction of hours	no	?		6
Irgapyrine i.v. Butazolidine i.v.	very weak	minutes to hours	no	?	effect is uncertain	7 8
Paraamino-benzoic acid oral	very weak	few hours	no	?	effect is uncertain	7
Novocain i.v.	weak	minutes to hours	no	?	effect is uncertain	7 9
Protamine sulfate i.v.	weak to strong	minutes	to some extent	neutralizes anti-plasmin? Activates plasminogen?	effect is uncertain	10 7 11
Typhoid vaccine (not shock free)	strong	hours	no	?	considerable side reactions	12

ulins, prepared from 0.3 ml. of plasma, were dissolved in 0.3 ml. of buffered saline and clotted with 0.01 ml. of thrombin. (e) Determination of the lysis time of a plasma clot made according to "b," but after addition of urofibrinolysokinase¹⁷ of standard activity. (f) Fibrin plates: The bovine plates were made based on the procedure of Lassen¹⁸ of the Astrup-group. The plasma plates were developed by us. Unheated bovine plates: Ten milliliters of a 0.6 per cent bovine fibrinogen (Armour) were dissolved in buffered saline in an Erlenmeyer flask, pH adjusted to 7.4 if necessary, and chilled, 0.1 ml. of thrombin solution was added, mixed, and the mixture rapidly poured into a carefully leveled flat-bottom Petri dish. Clotting occurs within 30 seconds. The plate was incubated for 10 minutes at 37 C. before use. Heated bovine plates: These were prepared as indicated using 0.4 per cent bovine fibrinogen and heated for 45 minutes at 85 C. after the initial incubation. Human plasma plates: Blood was drawn with siliconized equipment and spun

at 900 g at 4 C. for 10 minutes. Ten milliliters of plasma so obtained were either poured into siliconized Petri dishes and allowed to clot spontaneously, or 0.04 ml. of thrombin solution was added before placing the plasma in the dishes.

The recalcification method as indicated under 'a' was chosen to avoid dilution of the specimen, which is bound to bring about disturbance in the equilibrium inhibitors, activators of both clotting and fibrinolytic components. The recalcification times obtained by the above method are roughly comparable with the Lee-White times.

Method 'b' was the standard method used for measurement of fibrinolysis throughout the study. For detection of weak lysis tendency, method 'c' was used, early in the investigation.

Studies were carried out with 7 patients, who showed marked induced fibrinolysis by Schultz et al.¹⁹ of the Research and Development Unit of the Fitzsimons Army Hospital, Denver, using the synthetic substrate method.

Antifibrinolysin-Estimation. For this estima-

tion the supernatant fluid remaining after removal of euglobulins was used. It was free of fibrinolytic activity, even when prepared from very fibrinolytic plasma specimens. A mixture of 0.05 ml. of 1 per cent bovine fibrinolysin (Parke, Davis) and 1 ml. of 0.1 per cent bovine fibrinogen (Armour) treated with barium sulfate, was clotted with 20 units of bovine thrombin (Armour). A lysis time of 4 to 5 minutes resulted at 37 C. For the estimation of antifibrinolysin activity 0.05 ml. of albumin solution was added and the lysis time was noted. With high anti^hfibrinolysin titer no lysis occurred in 24 hours. The average lysis time in the presence of the above amount of albumin solution was 1 to 2 hours.

All blood specimens were processed immediately after venipuncture for fibrinolysis studies. In most instances, the tests with a, b, c, e, and f were started within 20 minutes, d, within 45 minutes.

Procedure with Patients. The pyrogenic material was injected intravenously in all instances with an injection speed of 20 seconds per ml. The patients were not fasting. Bed rest was ordered as long as the temperature was over 37.5 C. Temperature and blood pressure were taken every 30 minutes. Of 67 patients, 36 were women in their second to fourth postpartal day in the age group 17 to 37. The rest were female and male medical and surgical patients, ages 15 to 68.

Pretreatment. The great majority of patients were premedicated in the hope of reducing side reactions and fever. Pabirin or Ascriptin were used according to the following schedule: Pabirin: 4 a.m., 0.6 Gm.; 6 a.m., 0.6 Gm.; 8 a.m., intravenous injection of pyrogen; 8:30 a.m., 0.9 Gm.; 11 a.m., 0.9 Gm. Ascriptin: 10 p.m., 0.6 Gm.; 2 a.m., 0.6 Gm.; 6 a.m., 0.9 Gm.; 8 a.m., intravenous injection of pyrogen, and 0.9 Gm.; 11 a.m., 0.9 Gm. (2 p.m., 0.9 Gm., if necessary). In some instances Aminopyrine was used, which seemed however to have no advantage over Pabirin or Ascriptin. Ten-milliliter samples of citrated blood were taken before and at intervals after injection and were processed immediately for fibrinolysis studies as indicated. The temperature was taken under the tongue with a TRI-R electronic thermometer.

RESULTS

The pertinent data of all patients treated with intravenous pyrogens are summarized in

table 2.* In the following, some results of particular interest will be emphasized:

Onset and Duration of Pyrogen-Induced Fibrinolysis and Its Relation to Dosage

Euglobulin and Plasma Lysis. In serial determination maximal fibrinolytic activity always occurred between 90 and 120 minutes after intravenous injection of the pyrogen, irrespective of the intensity of the fibrinolysis. We found it best to test for peak activity at 105 minutes. The total period of fibrinolysis increased with increasing intensity (figs. 1 and 2).

The speed of fibrinolysis and its relation to the time elapsed after injection of the lipopolysaccharides is clearly demonstrated by coagulograms (figs. 1 and 2). They also indicate that fibrinolysis is not a linear process with respect to time, but proceeds at varying rates. The basic pattern of fibrinolysis is that of a slow onset followed by increasing disintegration speed of the coagulum, which then remains fairly constant for some time, and ends in a final slowdown.

A dose of 0.15 to 0.2 μ g. of 1064 or of 200 to 350 μ g. of 1083 regularly (38 out of 38 patients) induced fibrinolysis except in 2 intensively heparinized patients (no. 15 and 16), where negative results were obtained using the euglobulin technic alone. We found later that the lysis of euglobulin in the presence of heparin may be misleading. These and related observations will be reported elsewhere.²⁰ The euglobulin technic is otherwise very helpful in detecting lysis tendency when no lysis can be observed on 24-hour incubation in the plasma or by coagulographic recording. Figure 3 illustrates this effect when injections of 100 μ g. of 1083 were used.

This amount of pyrogen induces marked fibrinolysis in less than half of the cases. It appears from the 60-minute sample in figure 3 that the euglobulin control in contrast to the undiluted plasma sample, which exhibits no fibrinolysis at all.

Figure 3 demonstrates that the weak lysis tendency is shown much better by the euglob-

*Table 2 has been deposited with the ADI-Auxiliary Publications Project, Photoduplication Service, Library of Congress. Copies may be obtained from this service (ADI document no. 5364) for \$1.25.

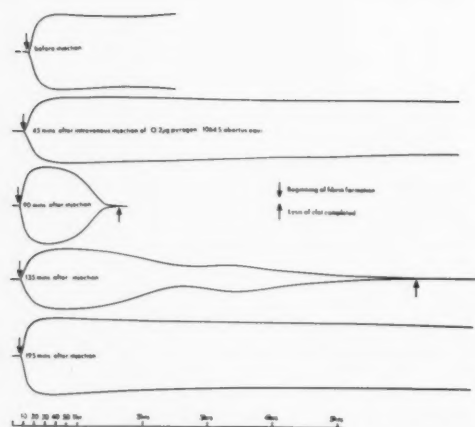


FIG. 1. Coagulographic pattern of plasma fibrinolysis after intravenous injection of 0.2 μ g. of pyrogen 1064.

ulin technic than by undiluted plasma lysis. Table 2 gives 11 examples (no. 4, 25, 29, 31, 32-34, 51, 61, and 65) in which injection of small amounts of pyrogen shortened considerably the 105-minute lysis time of the euglobulin sample, as compared with the preinjection euglobulin control. There is thus demonstrated an increased lysis tendency by the use of pyrogen not detectable using undiluted plasma alone.

Figure 4 illustrates again the relation of euglobulin to undiluted plasma lysis time. Here the results of all tests done during pyrogen treatment of patient no. 14 are shown graphically. This patient had a marked fibrinolysis without any significant temperature elevation. The 5-hour specimen showed a reduced euglobulin lysis time and there was no lysis in the plasma specimen at all; lysis was detectable only by the euglobulin technic. Figure 4 shows also another phenomenon which we call the rebound effect, and which is discussed in the following paragraph.

Rebound Effect and Tolerance. The euglobulin lysis time of the last 2 samples of the serial determinations of patient no. 14 represented in figure 4 is longer than that of the preinjection sample. This is a characteristic finding in all our cases where serial euglobulin determinations were made. It was

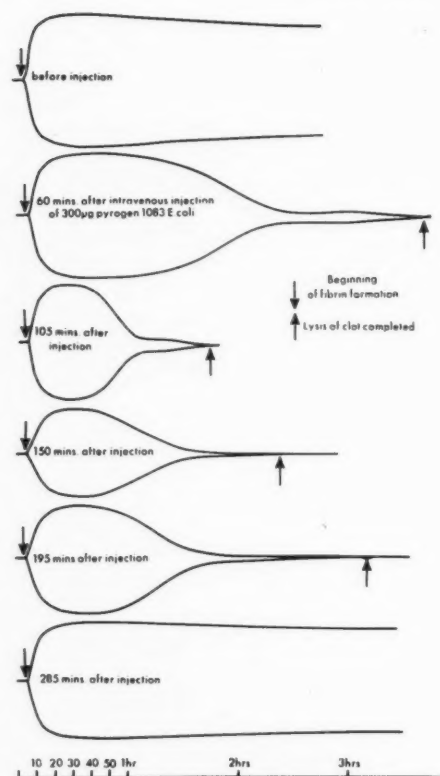


FIG. 2. Coagulographic pattern of plasma fibrinolysis after intravenous injection of 300 μ g. of pyrogen 1083.

observed that several postinjection euglobulin samples, after the fibrinolytic reaction had subsided, took considerably longer to lyse than the control. This prolongation was frequently still present after 24 hours (patients no. 56, 58, and 59). The reduced tendency to lyse could also be observed when a standard amount of urofibrinolysokinase had been added to the serial specimens. The fibrinolysis induced by urofibrinolysokinase in some samples was always less intensive after disappearance of the pyrogen-induced fibrinolysis than that in the preinjection control samples. This resistance to lyse spontaneously (euglobulins) or after addition of activator (urofibrinolysokinase) to undiluted plasma is temporary.

A second injection of pyrogen given 105

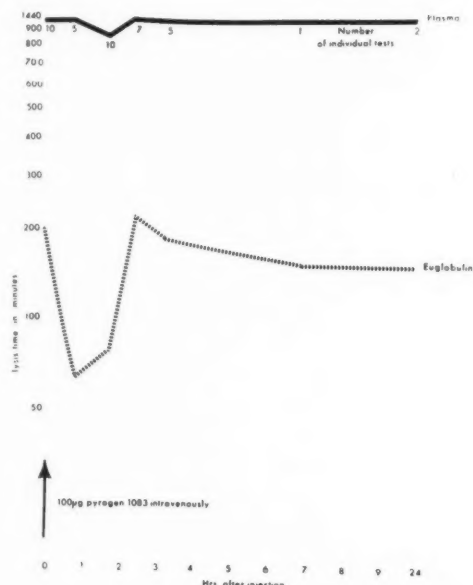


FIG. 3. Comparison of plasma and euglobulin lysis time in serial determinations after intravenous injection of 100 µg. of pyrogen 1083.

minutes after the first one (first dose being 100 µg., second dose being 50 µg., patients no. 62-66, or 150 µg., no. 67 respectively) did not delay the "rebound" effect or prolong the lysis period. Lysis could be produced with the dose used in only one (no. 63) out of 6 cases during the rebound effect.

At present we have no satisfactory explanation for the rebound effect that disappears in 24 to 48 hours. Our results tend to rule out any influence of antifibrinolysin. One of our cases was particularly spectacular. A female patient (no. 11) exhibited spontaneous fibrinolysis in the preinjection specimen, the euglobulin lysis time being 31 minutes and plasma lysis time 12 hours. A very marked lysis of 6 hours' duration was induced by 300 µg. of 1083. Twenty-four hours after the injection, however, the euglobulin lysis time was prolonged to 193 minutes, which is within normal limits, and there was no lysis in the plasma upon 24 hours' incubation. The rebound effect was strong enough to abolish a pre-existing considerably

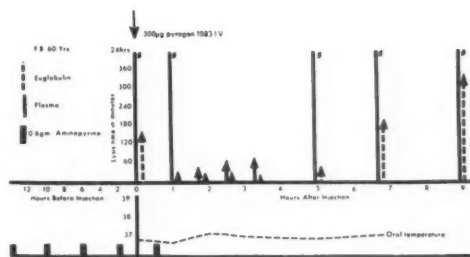


FIG. 4. Euglobulin and plasma lysis in a pretreated individual who exhibited marked fibrinolysis without fever after intravenous injection of 300 µg. of pyrogen 1083.

increased lysis tendency.

Differing from the rebound effect is the tolerance. It is well known that fever and accompanying reactions tend to diminish when the same amount of pyrogen is injected repeatedly in 24-hour intervals. The results of our studies indicate that the fibrinolytic reaction tends to become less and less marked after repeated injections in 24-hour intervals as well. For the determination of the lysis tendency the euglobulin technic had to be used because frequently the second injection brought about a much less intensive fibrinolysis of the undiluted plasma specimen or even failed to induce any plasma lysis. No plasma lysis at all was induced by the third injection. The euglobulin technic here still picks up increased lysis tendency no longer demonstrable with plasma. These conditions are well demonstrated by the data of patients no. 55 and 57-61. Preliminary studies indicate that the period of tolerance may not last longer than 1 week (patients no. 52-54) after the last injection. Possibly it might be broken through by larger pyrogen dosage for the second and still larger for the third injection.

In 25 cases serial estimation of antifibrinolysin was made. A characteristic example of 1 patient (no. 45) is given in figure 5. The arrows pointing downward in the lower row show the antifibrinolysin activity as expressed in minutes of lysis time of the system, diluted albumin-fraction bovine-fibrinolysin bovine-fibrinogen-thrombin. There was

TABLE 3.—*Influence of Incubation on Lysis Time of Fibrinolytic Plasma and the Corresponding Euglobulin Fraction*

Incubation in min. at 37°C.	Lysis time of undiluted plasma (min.)	Lysis time of euglobulins (min.)
0	48	20
20	63	8
30	not done	6
50	102	no clot

TABLE 4.—*Comparison of Lysis Time of Clots from Diluted (1:19) and Undiluted Plasma; i.v. Injection of 300 µg. of Pyrogen 1083. Serial Samples*

Time after injection	Lysis time plasma	
	undiluted	diluted
0	>24 hrs.	>24 hrs.
90	24 hrs.	>24 hrs.
105	45 min.	180 min.
150	63 min.	240 min.
180	75 min.	240 min.
240	24 hrs.	>24 hrs.

TABLE 5.—*Reaction and Fibrin Formation Times in Plasma from Fourteen Fibrinolytic Patients. Each Figure Represents the Average Value of Fourteen Individual Measurements*

Min. after injection of pyrogen 1083	0	60	105	150	195
Patients with lysis	0	7	14	7	4
Reaction time min.	9.4	9.2	7.2	6.7	6.3
Fibrin formation ^a	8	5.5	4.5	4.2	6.6
Half completed ^b	17.4	14.7	11.7	10.9	12.9

a. Time elapsed from start of fibrin formation min.

b. Time elapsed from start of clotting (min.).

TABLE 6.—*Maximal Temperatures of Thirty-Eight Patients with Less Than 180 Minutes Lysis Time after i.v. Injection of 100 to 300 µg. of Pyrogen 1083. All Patients were Pretreated*

Temperature range	Number of patients
Normal to 37.5	4
37.6 to 38.0	6
38.1 to 38.5	8
38.6 to 39.0	9
39.1 to 39.5	3
39.6 to 40.0	3
40.1 to 41.0	5
	38

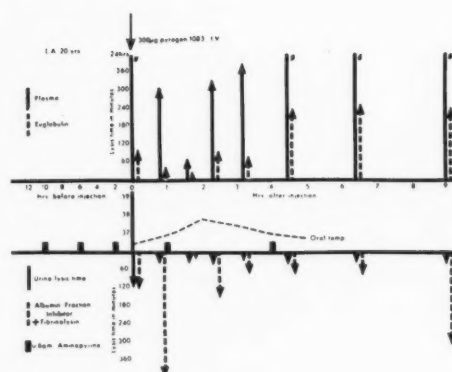


FIG. 5. Intravenous injection of 300 µg. of pyrogen 1083. Trend of fibrinolytic activity of plasma and euglobulin. Note rebound effect of euglobulin lysis time. Trend of antifibrinolysin activity.

no spontaneous fibrinolysis in the control without fibrinolysin, when the albumin fraction was prepared from the most active fibrinolytic samples. Figure 5 shows that the antifibrinolysin activity increases considerably 60 minutes after intravenous injection of the pyrogen. The antifibrinolysin activity is then reduced, but does not disappear entirely even at the peak of fibrinolytic activity. Subsequently it returns with some fluctuations to values exceeding the pre-injection levels.

Of interest is the "rebound effect" producing a euglobulin lysis time in samples 6, 7, and 8 considerably longer than those of the preinjection sample. The rebound effect of sample 6 coincides with a reduced antifibrinolysin activity. This observation, made repeatedly, led us to the conclusion that antifibrinolysin activity is not related to the rebound effect. The general pattern of antifibrinolysin activity in patients with pyrogen-induced fibrinolysis is basically that shown in figure 5. There is commonly a rise in activity in the first hour after injection, then a reduction of activity at peak fibrinolysis and for a short time thereafter. Then after more or less pronounced fluctuations control values are obtained in 24 hours. In these same cases no changes in antifibrinolysin

were seen in spite of the presence of a marked lysis.

There was no indication that the status of antifibrinolysin activity before pyrogen treatment has any bearing on the outcome of the intensity of the induced fibrinolysis. Marked fibrinolysis could be induced at any antifibrinolysin activity.

Effect of Incubation of Fibrinolytic Plasma and Euglobulin. Plasma and euglobulin samples of the most active 105-minute specimens were incubated for various times, clotted, and the lysis time measured. Results, as shown in table 3 are characteristic. As the incubation time increased the lysis time of the plasma also increased due to inactivation by the inhibitor of the fibrinolytic enzyme present in the plasma. In contrast the lysis time of the euglobulin fraction, which is essentially free of inhibitors, decreases on incubation, due to partial digestion of fibrinogen. In the euglobulin sample chosen for table 3, no clot was obtainable after 50 minutes of incubation, since the fibrinogenolysis was complete. For comparable and clearly defined results both plasma and euglobulin samples should be processed immediately.

Lysis in Undiluted Serum versus Lysis in Diluted Serum. It has been recommended that the dissolution of clots obtained from diluted plasma (1:19) be observed to discover weak lysis tendency.^{21, 22} Clots from undiluted plasma may show no noticeable lysis under these conditions, whereas those from diluted plasma do show lysis. It was thought that this phenomenon may be due to dilution of the inhibitor to ineffective levels in the diluted plasma. In our studies however the diluted samples consistently required much longer to lyse (if they lysed at all in 24 hours) than the undiluted samples prepared from the same plasma. A representative example is given in table 4.

The difference in lysis time of diluted and undiluted plasma during pyrogen-induced lysis can be interpreted by the assumption that the fibrinolysis is caused by the release of an activator for plasminogen, the activity of which is reduced by dilution.

Pyrogen-Induced Fibrinolysis and Clotting. Serial coagulograms were run of a number of patients who exhibited marked fibrinolysis. To obtain the complete sequence of data shown in table 5, only those patients were selected in whom fibrinolysis, though marked, started after the fibrin formation was completed. The lysis of the most active sample frequently started before completion of fibrin formation, making it impossible to obtain complete data. For technical reasons it was not always possible to obtain more than 5 consecutive coagulograms of a single patient. The reaction time (the time elapsed from recalcification to the measurable start of fibrin formation) and also the time required to form half of the fibrin were measured. It was found that the reaction time was considerably reduced during and sometimes after the fibrinolytic period. A marked increase in the speed of fibrin formation was concomitantly demonstrable. The deviations from preinjection values of the reaction and fibrin formation times can reach considerable proportions as is shown in table 5.

Table 5 shows the progressive shortening of the reaction time and fibrin formation time during pyrogen induced fibrinolysis. The greatest intensity of acceleration of clotting is reached 150 minutes after injection of the pyrogenic material. At this time the fibrinolytic activity had already begun to subside. At this moment the fibrin formation time is reduced to nearly half of its preinjection value. The 195-minute sample reveals that the fibrin formation time begins to shift toward preinjection values, whereas the reaction time has no tendency to normalize at this point. For cases in which we could obtain a complete coagulogram series, return to preinjection values for reaction and fibrin formation time occurred at or after the fourth hour following injection.

Relation of Temperature Elevation to Intensity of Fibrinolysis. No close relation was found between the height of the fever and the speed and intensity of fibrinolysis. Marked fibrinolysis, i.e., less than 180 minutes lysis time of undiluted plasma, occurred at any body temperature (table 6). In this table the

fibrinolysis time of the undiluted plasma specimen obtained 105 minutes after injection of the pyrogens and the highest temperatures reached in the postinjection period are recorded. The fibrinolysis peak always preceded the fever peak.

Eleven patients developed fever over 38 C. and exhibited poor fibrinolysis, lysis time of undiluted plasma being longer than 180 minutes, and an additional 4 had fever over 38 C. with no fibrinolysis at all. One patient (no. 56) who was treated for occlusion of the internal carotid artery, showed fibrinolysis after pyrogen injection. He developed spontaneous fever above 41 C. 36 hours later. During this temperature elevation the blood showed no fibrinolytic activity.

Pretreatment with Antipyretics and Their Interaction with Fibrinolysis. We have found that complete suppression of fever or side reactions by premedication did not result in a reduction of the fibrinolytic response. On the contrary we found that pretreatment may even enhance the fibrinolytic reaction.

One series of 23 patients received 100 to 150 μ g. of 1083. Of 7 unpretreated patients in this group, only 2 showed fibrinolysis, whereas of 16 pretreated patients 13 exhibited fibrinolytic reaction. In this series a combination of Pabirin and additional Ascriptin was administered, since it had previously been shown (see table 1) that a high dosage of paraaminobenzoic acid alone may induce some fibrinolytic activity in man.

General Observations on Pyrogen-Induced Reactions. The temperature started to rise 30 to 60 minutes after the intravenous injection of the pyrogen, reached a maximum in about 3 to 4 hours, and returned to normal within 3 to 6 hours. The rise in temperature was preceded by the usual systemic manifestations of fever, which were minor in most instances. Nausea was classified as a severe side reaction and vomiting as very severe. After all pyrogen-induced reactions had subsided, the patients expressed a sense of well-being and frequently became more or less euphoric. This fact should be considered

in evaluating the subjective symptoms during thrombosis treatment with pyrogens. Of 57 patients treated with 100 to 300 μ g. of 1083, 2 had a very severe side reaction, 5 severe, 17 moderate, 26 mild, and 7 none at all. Three patients of the 7 classified as "very severe" and "severe" were not premedicated.

Blood Pressure and Blood. The blood showed the known response to pyrogens: lymphopenia, eosinopenia, and leukopenia followed by leukocytosis. We have seen no critical fall of blood pressure; however, hypertensive patients were not treated. In some instances there was a drop of 10 to 15 mm. Hg for a few minutes in the first 2 hours after injection. One patient (no. 56) showed marked transitory hypotension.

Miscellaneous. Paracoagulation. In several instances it was observed that a narrowing of the coagulogram due to fibrinolysis was interrupted by a new widening followed by a narrowing as fibrinolysis proceeded to completion (fig. 1, 135-minute sample). In some cases, even after a complete lysis, a new minor clotting took place followed by a new lysis. This phenomenon of a new partial coagulation, after the sample had lysed completely, was first observed by Derechin²³ and designated as paracoagulation. At present we explain this as an incomplete transformation of fibrinogen into fibrin in the sample and by a subsequent release of the thrombin adsorbed on fibrin during fibrinolysis. This released thrombin then clots the remaining fibrin.

Fibrin Plates. The active 105-minute sample induces fibrinolysis on plasma plates made from the patient's preinjection plasma. This phenomenon enabled us to study the action of anticoagulants on human fibrinolysis. Preliminary results have been reported elsewhere.²⁴ It was also found that the lytic plasma samples were as active against heated bovine plasma plates as against unheated plates, indicating that the final activity of the lytic samples is primarily due to plasmin itself.

Synthetic Substrates. The synthetic sub-

strates Tosylargininester and Lysinester were not attacked even by the most active plasma samples. These substrates are easily split by purified plasmin. It is assumed that inhibitors present in plasma suppress the esterase activity of the fibrinolytic enzyme. Details have been reported by Schultz and co-workers.¹⁹

Induction of Lysis in Control Samples. The active 105-minute sample of undiluted plasma induced fibrinolysis in the preinjection control plasma samples. The required concentration of the active plasma preinjection plasma for a fibrinolysis in 24 hours varied between 5 and 30 per cent depending on its activity. Lysis was also induced in rabbit plasma, but much higher concentrations were required.

Storage. The activity of the frozen samples decreased only gradually when frozen at -15 C. Half of the activity was found in 1 sample after 10 months' storage.

Animal Studies. It was not possible to induce fibrinolysis with pyrogens used in this study in rabbits and dogs.

DISCUSSION

The injection of highly purified pyrogens enables us to induce a marked fibrinolysis in human beings. Pyrogen injection, which is only one of many stimuli that can bring about fibrinolysis in man, is the most potent of nonenzymatic or nonproteolytic nature known at present. The stimulating material may be of endogenous or of exogenous origin. In the case of endogenous origin, the pathologic release of an activator for plasminogen (from prostate, uterus, or lung) is the probable method of activation. The mechanism of action of such exogenous-stimulating materials as epinephrine, acetylcholin, anesthetics,²⁵ butazolidine, paraaminobenzoid acid, pituitary extracts, and other agents has not been clarified. None of these materials has any fibrinolytic or plasminogen-activating properties *in vitro*. According to our observations the activity of antiplasmin plays no prominent part in the appearance of fibrinolytic activity after administration of these substances, provided the stimulus is strong

enough. Activation of the fibrinolytic enzyme to a minor degree only may very well be masked by the presence of strong inhibitor. On the other hand more plasminogen can always be activated in a given amount of blood than the inherent antiplasmin is able to inactivate, provided the activation is carried far enough. We assume that the nonenzymatic stimulating exogenous compounds trigger the release of the activator of plasminogen from the tissue, either by acting directly on the cell membrane or by the intermediate of a central regulating mechanism. We were unable to demonstrate clearly the presence of an activator in our studies, but this does not exclude the possibility of its presence. In experiments using an activator isolated from human urine we were able to demonstrate that the activation of plasminogen proceeds more rapidly as the concentration of activator in the reaction mixture is increased. It may well be that the pyrogen injection brings about a sudden rise in the concentration of the activator (or proactivator?) in the blood resulting in a rapid and extensive activation of plasminogen to plasmin, which masks the concomitant presence of the activator itself. The results of the fibrin plate studies indicate that activated plasminogen is present, which could only occur by activation of its precursor. We are convinced that the definitely longer time of the diluted samples in contrast to that of the undiluted ones is indicative of the concurrent presence of an activator that is considerably reduced in activity when diluted. The lysis time of the clot from diluted plasma is primarily determined by plasmin already activated. This harmonizes with our earlier observation^{26, 27} that by injection of acid-activated swine plasmin into rabbits we brought about a fibrinolysis that is only detectable in diluted samples (in which the antiplasmin is diluted) and not in undiluted ones. It is hoped that future studies will reveal the details of the mechanism of induced fibrinolysis and should in particular clarify whether Astrup's²⁸ and Müllertz's²⁹ proactivator takes part in the induction of fibrinolysis in the human circulating blood by unspecific stimuli. It might then

be expected that therapeutic lysis can be induced by non-fever-producing substances.

The findings reported in this paper raise anew the question of the interaction of fibrinolytic enzyme and clotting factor. It was observed in coagulographic studies on earlier occasions³⁰ that induction of fibrinolysis in human blood *in vitro*, either by streptokinase of swine or bovine fibrinolysins, is always combined with earlier onset of the beginning of fibrin formation. Serial coagulograms before and during pyrogen-induced fibrinolysis reveal the same clotting pattern. Studies are under way to investigate the mechanism involved. It is thought that the increased coagulability during and after pyrogen lysis is not due to the pyretic action itself, but to the lysis tendency induced by them. The earlier onset and increased speed of fibrin formation during pyrogen-induced fibrinolysis represent a period of increased coagulability and might possibly have some bearing in thromboembolic conditions. Simultaneous heparin treatment is, at least theoretically, therefore indicated. Anticoagulant treatment should be continued after the fibrinolytic reaction has disappeared, since fibrinolysis does not suppress hypercoagulability itself (when present), but is only supposed to eliminate its most dangerous result, the intravascular clot. Persistent hypercoagulability after induced lysis can abolish its beneficial effect by allowing formation of new clots. However, excessive heparin concentration should be avoided, as we found with various techniques that 125 and 525 $\mu\text{g.}$ of heparin per ml. of plasma inhibit fibrinolysis in the test tube in contrast to 1, 5, and occasionally 25 $\mu\text{g.}$ of heparin, which may enhance fibrinolysis.²⁰ No investigations have been made to our knowledge to determine the effect of fibrinolysis on heparin activity. Theoretically it might be assumed that in heparinized fibrinolytic blood the hemostasis is more impaired than in heparinized blood alone. The fibrin formation proceeds at a very slow rate in heparinized blood (at heparin concentrations that delay but do not completely prevent clotting) with formation

of a few strands at the beginning. In this situation, even a weak fibrinolytic reaction may be sufficient to disintegrate those few strands and delay further the formation of a clot firm enough to produce hemostasis.

In our series fibrinolysis was studied in the dissolution of clots that were formed in a fibrinolytic milieu, thus ensuring a thorough distribution of the enzyme within the clot. This could rarely happen in the human origin. *In vivo* the enzyme must work on a clot already formed. It can attack only from the exterior and not from within. These conditions are partially duplicated by the use of fibrin plates. To study the therapeutic possibilities of the fibrinolytic system further, standard clots *in vitro* formed in the absence of fibrinolytic enzymes must be used. These studies are currently under way in our laboratories.

Our preliminary clinical observations combined with the findings of other students of the problem in human beings and in animals indicate that the clot already formed in the circulatory system can very well become smaller or disappear completely, if the circulating blood possesses marked fibrinolytic activity. It seems also to be true that the fibrinolytic disintegration of the preformed clot continues for some time after disappearance of fibrinolysis in the circulating blood. Extensive studies will be required to substantiate these preliminary observations. The great affinity of the fibrinolytic enzyme for fibrin is well known. One of the early fibrinolytic preparations was obtained from autolyzed fibrin.³¹

The data presented in this paper indicate that very marked fibrinolysis can easily and regularly be induced in human beings by injecting purified pyrogens. In none of our cases with marked induced lysis did bleeding occur. This was particularly remarkable for one case with low fibrinogen and prothrombin levels due to advanced liver cirrhosis (patient no. 5) and for all the postpartal patients who showed no increase in the blood content of their lochia. In retrospect these observations are not too astonishing for the

following reason. The fibrinolytic reaction in our series was induced by 2 pyrogens of different origin. Furthermore, Italian investigators have used pyrogenic typhoid vaccine for fibrinolytic treatment of thromboembolic disorders. We are entitled to assume that other pyrogens will have similar effects with possible side reactions. One wonders how many patients might have had a more or less marked fibrinolysis since the introduction of fever therapy by the injection of pyrogenic material.

At present we have limited our studies on pyrogen-induced fibrinolysis and its therapeutic applications to those conditions in which fever therapy is not contraindicated. This limitation excludes many situations in which attempts to dissolve a clot would be highly desirable as in coronary occlusion. On the other hand, we are in a position for the first time to induce a very marked fibrinolysis, with a high rate of success without resorting to enzymatic fibrinolytic material in human beings. We are thus able to study the phenomenon of fibrinolysis in human subjects more extensively and can acquire information useful in achieving the ultimate goal of safely bringing about the dissolution of intravascular clots.

SUMMARY

The mechanism of pyrogen-induced fibrinolysis has been studied in 67 individuals. Two-tenths of a microgram of protein-free pyrogenic lipopolysaccharides from *Salmonella abortus equi* or 300 μ g. from *Escherichia coli* (acetylated form) induces in 60 to 90 minutes after intravenous injection a very marked fibrinolysis lasting for 60 to 240 minutes in man. Clots of samples taken at peak activity (105 minutes) dissolve in less than 3 hours. There is frequently a reduction of antifibrinolysin activity during the fibrinolytic phase. Concomitant treatment with antipyretics does not diminish the fibrinolytic response. The spontaneous lysis time of euglobulins is prolonged after fibrinolytic activity has subsided. At this time more urofibrinolysokinase is required to induce lysis in the test tube. Eu-

globulin clots prepared from fibrinolytic samples undergo fibrinogenolysis. Repeated daily injections gradually became less effective in producing fibrinolysis. Induced fibrinolysis in patients with thrombophlebitis gave encouraging results.

SUMMARY IN INTERLINGUA

Le mechanismo del induction de fibrinolyse per injectiones de pyrogeno esseva studiate in 67 individuos. Duo decimos de un microgramma de aprotinice lipopolysaccharidos pyrogenic ab *Salmonella abortus equi* o 300 μ g. ab *Escherichia coli* (forma acetylate) induce, intra 60 a 90 minutas post lor injection intravenose in humanos, multo marcate grados de fibrinolyse que dura inter 60 e 240 minutas. Coagulos de specimens obtenite al tempore del activate maximal (i.e. post 105 minutas) se dissolve in minus que 3 horas. Il occurre frequentemente un reduction del activate antifibrinolysin durante le phase fibrinolytic. Tractamento concomitante con antipyreticos non reduce le responsa fibrinolytic. Le tempore del lyse spontanee de euglobulina es prolongate post que le activate fibrinolytic ha subsidite. A iste tempore, plus urofibrinolysokinase es requirite pro inducer lyse in vitro. Coagulos euglobulinie preparate ab specimens fibrinolytic experientia fibrinogenolyse. Repetite injectiones diurne deveniva gradualmente minus efficace in le production de fibrinolyse. Le induction de fibrinolyse in patientes con thrombophlebitis produceva resultatos incoragiante.

REFERENCES

1. INNERFIELD, I., SCHWARZ, A., AND ANGRIST, A.: Intravenous trypsin. Its anticoagulant, fibrinolytic and thrombolytic effects. *J. Clin. Invest.* **31**: 1049, 1952.
2. LAUFMAN, H., AND ROACH, H. D.: Intravenous trypsin in the treatment of thrombotic phenomena. *Arch. Surg.* **66**: 552, 1953.
3. CLIFFTON, E. E., SIEGEL, M., AND GROSSI, C. E.: Investigation of intravenous plasmin (fibrinolysin). Physiological and clinical effects. *Circulation* **14**: 919, 1956.
4. TILLET, W. S., JOHNSON, A. J., AND McCARTY, W. R.: The intravenous infusion of the streptococcal fibrinolytic principle into patients. *J. Clin. Invest.* **34**: 169, 1955.

5. SOULIER, J. P., AND KOUPERNIK, C.: Constance de la fibrinolyse au cours du choc acétyl-cholinique. *Le Sang* **19**: 362, 1948.
6. BIGGS, R., MACFARLANE, R. G., AND PILLING, J.: Observation on fibrinolysis. Experimental activity produced by exercise or adrenalin. *Lancet* **1**: 402, 1947.
7. VON KAULLA, K. N., AND DELLA SANTA, R.: Fibrinolyse thérapeutique sans choc. C. R. II Congrès de la Soc. Int. Europ. d'Hématol., Rome, Oct. 1952, Edizione Medica e Scientifica.
8. SIGG, B.: Die Behandlung der akuten Thrombophlebitis mit Irgapyrin. *Praxis* **41**: 1072, 1952.
9. DEUTSCH, E.: Discussion remark. *Wiener Ztschr. inn. Med.* **33**: 167, 1952.
10. HARTERT, H.: Discussion remark. Congress internal Med. Wiesbaden, 1952.
11. VON KAULLA, K. N.: L'inactivation de l'inhibiteur du ferment fibrinolytique. *Le Sang* **22**: 720, 1951.
12. MENEGHINI, P.: Terapia fibrinolitica e profilassi anticoagulante nelle malattie tromboemboliche. *Minerva Med.* **46**: 13, 1955.
13. EICHENBERGER, F.: Fibrinolyse nach intravenöser Injektion bakterieller Pyrogene. *Acta neuroveg.* **9**: 202, 1955.
14. WESTPHAL, O., AND LUEDERITZ, O.: Chemische Erforschung von Lipopolysacchariden gramnegativer Bakterien. *Ztschr. angewandte Chemie* **66**: 407, 1954.
15. VON KAULLA, K. N., AND WEIL, J.: Pyrogen induced fibrinolysis in man. *Fed. Proc.* **15**: 194, 1956.
16. —, AND WEINER, M.: Studies of coagulation and fibrinolysis by a new technique of continuous recording. *Blood* **10**: 362, 1955.
17. —: Methods for preparation of purified human thromboplastin and fibrinolysokinase from urine. *Acta haematol.* **16**: 315, 1956.
18. LASSEN, M.: Heat denaturation of plasminogen in fibrin plate method. *Acta physiol. scandinav.* **27**: 371, 1953.
19. SCHULTZ, R. L., MOORMAN, J. A., MATOUSH, L. O., AND LINCOLN, A. F.: Evaluation of synthetic substrate methods for clinical determination of fibrinolysis. *Proc. Soc. Exper. Biol. & Med.* **94**: 198, 1957.
20. VON KAULLA, K. N., AND MACDONALD, S. T.: The effect of heparin on components of the human fibrinolytic system. In preparation.
21. MACFARLANE, R. G.: Fibrinolysis following operation. *Lancet* **1**: 10, 1937.
22. —, AND BIGGS, R.: Observation of fibrinolysis. *Lancet* **2**: 862, 1946.
23. DERECHIN, M.: Caractères généraux de la paracoagulation fibrinolytique. *Rev. d'Hématol.* **10**: 35, 1955.
24. VON KAULLA, K. N., MACDONALD, S. T., AND TAYLOR, C.: The effect of heparin on fibrinolysis. *J. Lab. & Clin. Med.* **48**: 952, 1956.
25. —: Betrachtungen zur postnarkotischen Fibrinolyse. *Schweiz. med. Wchnschr.* **77**: 313, 1947.
26. —: Extraction of fibrinolytic enzyme from the blood. *Nature* **164**: 40, 1949.
27. —: Versuch zur Auslösung der Fibrinolyse durch Injektion fibrinolytischen Fermentes. *Klin. Wchnschr.* **29**: 422, 1951.
28. ASTRUP, T.: Fibrinolysis in the organism. *Blood* **11**: 781, 1956.
29. MÜLLERTZ, S.: Formation and properties of the activator of plasminogen and of the human and bovine plasmin. *Biochem. J.* **61**: 424, 1955.
30. VON KAULLA, K. N.: Antikoagulantien und Fibrinolyse. *Die Medizinische* No. 51: 1651, 1953.
31. ROSENMANN, M.: Über Fibrinolyse. *Biochem. Ztschr.* **112**: 98, 1920.



Inaccuracy of Wedge Pressure as an Index of Pulmonary Capillary Pressure

By JEROME P. MURPHY, M.D.

The wedge and left atrial pressures were compared in 12 subjects with congenital and acquired heart disease; all experiments were carried out with closed chest under basal conditions. A poor correlation between the wedge and left atrial pressures was noted in over half the patients. The wedge pressure is especially inaccurate in mitral stenosis with marked elevations in left atrial pressure.

IN 1906 MacCullum and his associates observed in dogs that pressure changes in the pulmonary venous system and the left atrium were transmitted to the pulmonary capillary bed and the end arteries of the lung. Subsequent investigators confirmed these findings and further demonstrated that the pulmonary venous and arterial capillary pressures were the same.^{1, 2} Direct measurements of the venous and arterial sides of the capillary bed in subjects with atrial septal defects showed that changes in venous pressure were quantitatively transmitted to the end arteries.³ These results strongly supported the concept that the pulmonary capillary bed offered little or no resistance to the retrograde transmission of the pulmonary venous pressure to the pulmonary end arteries.^{4, 5} Further investigations showed the pulmonary capillary pressure to be slightly higher but otherwise identical to the left atrial pressure.⁶ With the advent and widespread use of right heart catheterization a technic was evolved for measuring the pulmonary capillary pressure by means of the "wedge" method. This technic entails manipulating the cardiac catheter into a small pulmonary end artery so that all transmitted right ventricular pressures are damped completely. Whatever pressure is then recorded represents the pulmonary capillary pressure and transmitted pulsations from the left heart. A basic criterion for insuring a complete wedge is the sampling of

fully oxygenated blood when the catheter is in place.

Although certain theoretical objections have been raised to considering the wedge pressure and the pulmonary capillary pressures to be identical, there has been rather widespread acceptance of the basic concept that the wedge pressure is an accurate index of the pulmonary capillary pressure and hence of the pulmonary venous and left atrial pressures. Numerous studies requiring knowledge of the pulmonary capillary pressure as a factor have been carried out with the wedge pressure substituted for the pulmonary capillary pressure. The best known example of this is the hydraulic formula of Gorlin for calculating the mitral valve area. In its clinical application this formula utilizes accepted principles of hydraulics for the calculation of orifice size. When applied to the mitral area, the left atrial pressure is estimated by substituting the indirect wedge pressure.

Gorlin's formula

$$MVA = \frac{MVF}{31 \sqrt{"PC" - 5}}$$

MVA = represents mitral valve area in cm.²
MVF = represents mitral valve flow in ml. per second or cardiac output in ml. per second
 diastolic filling period in seconds/min.
 "PC" = pulmonary capillary pressure in mm. Hg (obtained by "wedge")
 5 = left ventricular diastolic pressure in mm. Hg, assumed
 $31 = C \sqrt{2g} = 0.7 \sqrt{1960}$

From the Department of Surgery and the Cardiopulmonary Laboratory of The Creighton University School of Medicine, Omaha, Nebr.

Recently catheterization of the left heart has evolved as a direct means of measuring the hemodynamic events in the chambers of the left heart. This technic provides a simple method for assaying the nature of the anatomic abnormalities of the diseased mitral and aortic valves. It also permits comparison of data obtained from catheterization of both sides of the heart and especially for the comparison of the wedge and left atrial pressures.

Connolly, Kirklin, and Wood⁷ obtained simultaneous wedge and left atrial pressures during mitral valvotomy in 5 patients. Although they noted a close correlation between the left atrial and wedge pressures, it is generally accepted that data obtained with the open chest and positive pressure anesthesia are often inaccurate and not reproducible. In 1953 Björk⁸ published the findings from the first group of patients studied by simultaneous catheterization of both the right and left hearts. Of the 9 patients studied 7 had complete data for comparison, including wedge and left atrial pressures. In 5 of these patients a close correlation between the wedge and left atrial pressures was noted. However, in 2 patients a significant difference between the wedge and left atrial pressure was seen. Similar disparities have been noted by other investigators.^{6,9} In a consideration of the relationships between the wedge and left atrial pressures, it would seem that any observed differences between these pressures cannot be regarded as representing real differences between the pulmonary capillary and left atrial pressures, particularly if the latter pressure is higher; in this event there could be no flow from right to left. The mean left atrial pressures must be lower than the pulmonary capillary pressure if unidirectional pulmonary flow is to occur. It follows, therefore, that any observed difference between the wedge and left atrial pressures represents a basic fault in measuring the left atrial pressure, or the wedge pressure is not a quantitative reflection of the pulmonary capillary pressure.

In an effort to resolve this problem a study was undertaken to compare the wedge and left atrial pressures in a group of patients from whom the necessary data has been obtained. Accordingly, the findings in a group of 32 patients subjected to left heart catheterization were reviewed. Twelve of these patients had complete right heart studies including authentic wedge pressures. Two of this latter group had examinations before and after mitral valvotomy, giving a total of 14 sets of data.

METHODS

All the patients were adults. The indication for catheterization in 3 of these was interatrial septal defect, while the remaining 11 cases had mitral or aortic disease. All studies were carried out under basal conditions with local anesthesia. The left heart studies were patterned after the method of Björk, with direct needle puncture of the left heart from the right paravertebral approach with a 15-cm. no.-17 needle. The ventricular pressures were obtained by direct puncture of this chamber rather than by passing a catheter from a needle in the left atrium. The pulmonary artery pressures were also obtained by direct needle puncture. The right heart catheterizations were done by a standard technic with the patient in the supine position. The zero setting for the pressure head during the left heart studies was the left atrium as marked on the chest wall at fluoroscopy. In the right heart studies the zero setting was 10 cm. from the table. All pressures were recorded by strain gage pick-up with photographic oscillographic recording. The wedge pressure was considered present at that point in the pulmonary arterial tree beyond which a no. 4 catheter would not pass but permitted sampling of fully oxygenated blood. The mean values were obtained by electric integration of the oscillographic tracings.

RESULTS

In the 14 sets of data obtained from 12 patients (table 1), 4 patients had no valvular disease, and the left atrial pressures in this group were normal or slightly elevated. In the remaining 8 cases with mitral or aortic valvular lesions, the left atrial pressure was elevated in all but 1. The mean and average values were compared; the latter values were found to be slightly lower. In the entire group a close correlation existed between the wedge

TABLE 1.—Data from Twelve Patients Having Fourteen Combined Heart Catheterizations

Patients	Pulmonary artery (mm. Hg)	Left ventricle (mm. Hg)	Left atrium CV wave/ Diastole (mm. Hg)	Pulmonary capillary pressure (mm. Hg)	Diagnosis
1	35/15	110/5	9/4	13/6	Interatrium septal defect
2	20/10	118/9	8/3	11/5	Interatrium septal defect
3	40/20	90/0	10/2	12/4	Interatrium septal defect
4	32/10	135/3	22/18	23/21	Mitral stenosis
5	18/15	140/6	15/9	15/9	Mitral stenosis
6	65/40	128/2	45/2	28/12	Mitral insufficiency
7	58/35	100/0	42/9	21/6	Mitral insufficiency
8	68/48	98/5	55/45	22/20	Mitral stenosis (pulmonary edema)
9	48/35	92/9	32/26	20/14	Mitral stenosis
10	45/32	105/8	28/22	19/9	Mitral stenosis
11	60/35	90/0	45/38	22/16	Mitral stenosis (pulmonary edema)
12	60/33	120/5	12/6	16/12	Case 11, postoperative
13	50/38	105/5	30/25	16/8	Mitral stenosis
14	52/34	130/0	8/5	10/6	Case 13, postoperative

Cases 1 to 5 have little or no wedge/left atrium difference. In this group there is only 1 case where the left atrial pressure was significantly elevated (over 15).

Cases 6 and 7 represent severe mitral regurgitation. The wedge pressure curve shows CV waves 21 and 17 mm. less than the CV waves in the left atrial pressure.

Cases 11 and 13 are preoperative and postoperative studies that show marked wedge/left atrial pressure differences preoperatively when the left atrial pressure was high but no difference or reversal of the ratio when the left atrial pressure drops to low ranges postoperatively.

Cases 8, 9, 10, and 11 are all "tight" mitrals with high left atrial pressures. In each case there is a significant wedge/left atrial pressure difference (9 to 33 mm.).

Cases 8 and 11 had clinical pulmonary edema with left atrial pressures compatible with this finding (over 35 mm. Hg) while the wedge was below 25 mm. Hg. (It is assumed that the colloid osmotic pressure component of the pulmonary capillary pressure averages 25 mm. Hg. Pulmonary edema should occur when the hydrostatic pressure exceeds 25 to 35 mm. Hg.).

and the left atrial pressure in 6 cases while a significant difference was noted in 8. The group with a marked difference between wedge and left atrial pressures included all cases in which the left atrial pressure was markedly elevated (over 20 mm. Hg). Furthermore the greatest differences occurred in those patients with the highest left atrial pressures. Of special note in this regard was case 11 in which the preoperative atrial pressure difference was 21 mm. Hg. Postoperatively a reversal of the ratio was seen. The other cases with studies before and after surgery showed a similar though less marked reversal. In the 2 cases of severe mitral insufficiency, the mean left atrial pressure exceeded the wedge pressure by 14 mm. Hg and 12 mm. Hg and the wedge tracing failed to show the height of the giant CV waves by 17 mm. Hg and 21 mm. Hg. In the patients with interatrial septal defects, the

pressure differences were slight and were due to slight increase in the wedge pressure. In cases 8 and 11, with clinical pulmonary edema, the left atrial pressure was in the range compatible with this clinical finding (in excess of 35 mm. Hg) while the wedge pressure was well below edema levels.

DISCUSSION

This study was undertaken to evaluate the wedge pressure as an index of the pulmonary capillary pressure. To this end the data from a group of 12 patients having 14 combined heart studies were analyzed. In approximately 50 per cent of the cases a significant difference between the wedge pressure and the left atrial pressure was noted. Since the left atrial pressure and the pulmonary capillary pressure are virtually identical, any indirect method for measuring this latter pres-

sure should give values similar to the more direct left atrial pressure. Failing this, one must assume that the wedge pressure is not an accurate quantitative index of the capillary pressure. The possibility that the left atrial pressures as obtained in this study were inaccurate was obviated by the use of the end-diastolic pressure in the ventricle as the 0 to 5 baseline. The most striking deficit in the wedge tracings was seen in those cases of mitral insufficiency in which the wedge contours mirrored the left atrial waves but failed to quantitate these wave values by significant margins. In patients studied while in pulmonary edema, it was noted that the left atrial values were in excess of the edema levels, while the wedge values were far below this line.

It is not the purpose of this study to explain or speculate on the inaccuracy of the wedge pressure but rather to demonstrate that such inaccuracy is present. Therefore it would seem logical to abandon an indirect technique subject to such a significant error in favor of the more exact method of left heart catheterization. The analysis of timed pressure curves from the left atrium allows for ready definition of the nature and domination of the valvular lesions present and provides accurate values for use in the hydrokinetic orifice formulas and other basic techniques for evaluation of pressure flow systems.

SUMMARY

A comparison of the wedge and left atrial pressures was carried out in a group of 12 patients with congenital and acquired heart disease. In 5 patients the left atrial pressures were not elevated and the wedge pressures showed similar contours and corresponding values. In 7 patients with elevated left atrial pressures the wedge pressures did not reflect these elevations with quantitative differences ranging from 9 to 33 mm. Hg. Two patients with clinical pulmonary edema and mean left atrial pressures of 50 and 41 had mean wedge pressures of 20 and 16.

In this study the wedge pressures paralleled the left atrial pressures when the latter were within normal ranges. The wedge pressures failed to reflect the left atrial pressures by significant values when the left atrial pressures were elevated.

SUMMARY IN INTERLINGUA

Un comparison del pression a cuneo e del pression sinistro-atrial esseva effectuate in un gruppo de 12 patientes con congenite e acquirite morbo cardiac. In 5 patientes le pression sinistro-atrial non esseva elevate, e le pression a cuneo monstrava simile contornos e correspondent valore. In 7 patientes con elevate pression sinistro-atrial, le pression a cuneo non reflecteva iste elevationes. Le differentias quantitative variava inter 9 e 33 mm. Hg. Duo patientes con clinic edema pulmonar e valore medie del pression sinistro-atrial de 50 e 41 habeva valore medie del pression a cuneo de 20 e 16.

In iste studio le pression a cuneo correspondeva al pression sinistro-atrial in tanto que istos se trovava intra le limites normal. Le pression a cuneo non reflecteva le pression sinistro-atrial e differiva ab illos significative mente quando le pression sinistro-atrial esseva elevate.

REFERENCES

- HELLEMS, H. K., HAYNES, F. W., DEXTER, L., AND KENNEY, T. D.: Pulmonary capillary pressure in animals estimated by venous and arterial catheterization. *Am. J. Physiol.* **155**: 98, 1948.
- LAGERLOF, H., AND WERKO, L.: Studies on the circulation of blood in man: VI. The pulmonary capillary venous pressure in man. *Scandinav. J. Clin. & Lab. Invest.* **1**: 147, 1949.
- CALAZEL, P., GERARD, R., DALEY, R., DRAPER, A., FOSTER, J., AND BURG, R. J.: XI. A comparison of the right and left auricular, capillary and pulmonary artery pressures in nine patients with auricular septal defect. *Bull. Johns Hopkins Hosp.* **88**: 20, 1951.
- DOW, J. W., AND GORLIN, R.: Pulmonary 'capillary' pressure as an index of left auricular mean pressure in dogs. *Fed. Proc.* **9**: 33, 1950.

5. HELLEMS, H. K., HAYNES, F. W., DEXTER, L., AND KENNEY, T. D.: Pulmonary capillary pressure in man. *J. Appl. Physiol.* 2: 24, 1949.
6. ANKENY, J. L.: Further experimental evidence that pulmonary capillary pressures do not reflect cyclic changes in left atrial pressure. *Circulation Research* 1: 58, 1953.
7. CONNOLLY, D., KIRKLIN, J. W., AND WOOD, E. H.: The relationship between pulmonary artery wedge pressure and left atrial pressure in man. *Circulation Research* 2: 435, 1954.
8. BJÖRK, V. O., MALSTROM, G., AND UGGLO, L. G.: Left auricular pressure measurements in man. *Ann. Surg.* 138: 718, 1953.
9. WIGGERS, C. J.: Pulmonary wedged catheter pressures. *Circulation Research* 1: 371, 1953.



Bedford, D. E., Sellors, T. H., Somerville, W., Belcher, J. R., and Besterman, E. M. M.:

Atrial Septal Defect and its Surgical Treatment. *Lancet* 1: 1255 (June 22), 1957.

One hundred consecutive patients with atrial septal defect (ASD) are presented with a review of the clinical features and complications. The anatomy of 3 types is described: atrioventricular (A-V) defects, fossa ovalis defects, superior caval defects. These may be present in combination. The now well-recognized clinical signs of ASD are reviewed—right ventricular type of cardiac impulse, systolic lift over the outflow tract of the right ventricle, pulmonary systolic thrill (20 per cent), pulmonary systolic murmur loudest in midsystole, an obviously split second sound. A diastolic murmur may be present (20 per cent). A short delayed tricuspid murmur is often heard (50 per cent). The A-V type may be suspected with (1) unusual cardiac enlargement in childhood, (2) physical underdevelopment, (3) pulmonary hypertension below the age of 20, (4) pansystolic murmur of mitral incompetence, (5) left ventricular hypertrophy in the electrocardiogram, (5) left-to-right shunt at the atrial and ventricular levels, (7) bacterial endocarditis, (8) complete heart block. Superior caval defects may show a localized dilatation of the superior vena cava. Catheterization shows arterialized blood in the superior vena cava. The complications of ASD are obstructive pulmonary hypertension (15 patients, 7 with reversed shunts), pulmonary stenosis (11), mitral stenosis (6), atrial fibrillation (10), anomalous pulmonary veins (10). Cardiac symptoms were mild to the age of 20, but a grossly enlarged heart was found in 20 per cent of the cases aged 20 to 40 years and 60 per cent of those over 40. Consequently, the authors believe that the proper time to close an uncomplicated fossa ovalis defect with a shunt of 2:1 or more is as soon as the diagnosis is established and preferably before the age of 20. Thirty of the 100 patients with ASD were rejected for surgery for 1 of the following reasons: (1) A-V defect, (2) reversed shunt with cyanosis (3) obstructive pulmonary hypertension, (4) systemic hypertension, (5) advanced age and poor condition. Closure of an ASD by open heart surgery under hypothermia was completed in 40 patients. There was only 1 fatality, following a second operation undertaken to resuture the defect. In another patient, an unsatisfactory result was due to deflection of the inferior vena cava into the left atrium. Among the remaining patients, the immediate results were satisfactory.

KURLAND

Severe Hemoptysis During Pregnancy Treated by Mitral Commissurotomy

By WILLIAM F. M. FULTON, M.B., Ch.B., M.R.C.P., AND
GEORGE SMITH, M.B.E., M.D., F.R.F.P.S.G., F.R.C.S.ED.

Pulmonary bleeding in mitral stenosis is not commonly regarded as an indication for operation. A case is reported in which mitral commissurotomy was performed during pregnancy primarily because of recurrent profuse hemoptysis. Some relevant points are briefly discussed.

PULMONARY apoplexy is a common symptom in mitral stenosis. According to Wood¹ such hemorrhages tend to be self-limiting and are never fatal. In his experience they are not in themselves an indication for mitral commissurotomy. Moreover, during pregnancy, operation is not often warranted and most of the reported cases were submitted to operation because of pulmonary edema.

CASE REPORT

The patient was a 19-year-old married woman of average build and nutrition. Five years previously she had left-sided chest pain and breathlessness on exertion. There was no history of acute rheumatism. Clinically, presystolic and middiastolic murmurs at the mitral area supported a diagnosis of mitral stenosis. In addition there was a systolic murmur at the aortic area and a short diastolic murmur at the left sternal border.

Breathlessness on exertion persisted with little change in severity during the ensuing 5 years. From her history, exercise tolerance was grade 2. Hemoptysis became a recurrent symptom some 3 years before the present illness. It was never severe and apart from these episodes she had neither cough nor sputum. Two years before admission, mitral commissurotomy had been considered elsewhere but was withheld, largely because of insufficient disability. The cardiac shadow at that time showed a mitral configuration (fig. 1).

Six days before admission on May 3, 1956, she started to cough up blood while walking but not exerting herself unduly. She thought that about 1 pint in all was lost. During the next few days 4 further hemoptyses of lesser severity took place.

On admission the patient was weak, pale, cyanosed, and dyspneic. She was about 4 months pregnant. The pulse was of small volume and regular at 120 per minute. The blood pressure was 95/55 mm. Hg. There was no peripheral

venous engorgement, no edema, and no palpable hepatic enlargement. The respiratory rate was 36 per minute. Rhonchi were present over both lungs but no fine crepitations were heard. A portable radiograph (fig. 2) showed increased vascularity of the left lung and collapse of most of the right lung. Much of her dyspnea was thought to be due to the pulmonary collapse.

As a result of the mediastinal shift a distinct cardiac impulse could be felt 8 cm. to the right of the midline. Nevertheless the predominantly right ventricular quality of the precordial systolic impulse could be appreciated. The apex beat was in the fifth left interspace, 8 cm. from the midsternal line. At the mitral area the first sound was loud, raised in pitch, and was preceded by a presystolic murmur. A well-marked opening snap was followed by a long diastolic murmur. There was a systolic thrill and murmur at the aortic area and a short early diastolic murmur down the left sternal border. It was considered that stenosis of the mitral valve was the main lesion and the cause of the hemoptysis. The electrocardiogram showed P waves consistent with this diagnosis and there was no evidence of right or left ventricular hypertrophy.

During the next 2 days the hemoglobin level fell from 11.2 to 9.1 Gm. per cent. Recurrent bleeding over a further 3 days brought the level down to 7.0 Gm. per cent. By this time the patient was exceedingly ill although the blood pressure was 90/55 mm. Hg. During the next 24 hours 1080 ml. of citrated blood were given slowly, raising the hemoglobin level to 8 Gm. per cent. Massive hemoptysis, however, recurred on the following day with a loss of 1200 ml. of bright red blood in the course of a few hours. Her condition was again critical. Although restoration of blood volume and hemoglobin was needed, the awareness of the role of congestion of the pulmonary circuit in producing further bleeding and pulmonary edema indicated extreme caution in further blood transfusion. Over the next 8 days slight hemopty-

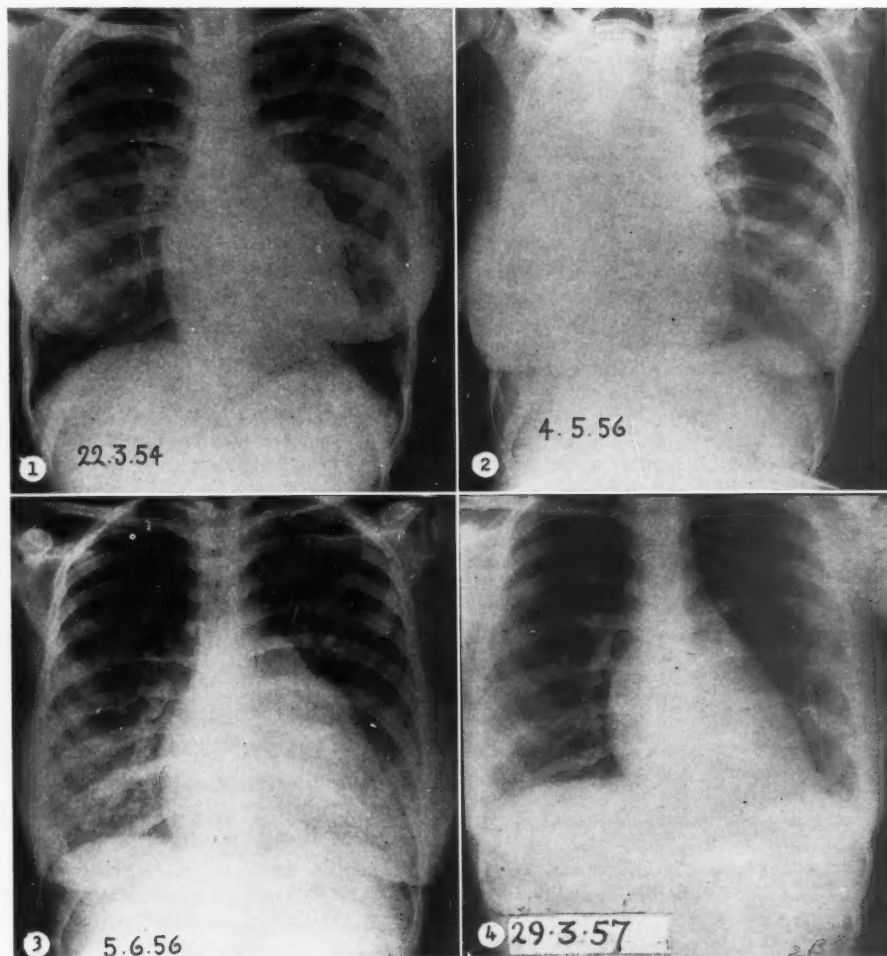


FIG. 1. March 22, 1954. Two years before admission.

FIG. 2. May 4, 1956. On admission. Collapse of right lung.

FIG. 3. June 5, 1956. Shortly before operation.

FIG. 4. March 29, 1957. Five months after delivery and 9 months after operation.

sis continued while she received the packed cells from 1620 ml. of blood. At the end of this period she was still critically ill and 2 further hemoptyses of about 300 ml. each took place.

At this point, conservative policy was abandoned. There seemed little likelihood that bleeding would cease and there were still more than 4 months of pregnancy to run. It was decided to perform mitral commissurotomy when her condition should have improved sufficiently to permit operation. By this time the collapsed right lung had expanded fully (fig. 3). Over the next 11 days the packed

cells from 2160 ml. of blood were transfused, causing the hemoglobin level to rise to 12 Gm. per cent. The general condition improved, pulse rate fell to 100 per minute, but the blood pressure did not rise above 90/60 mm. Hg. At the end of this time a further hemoptysis of about 300 ml. occurred and as soon as bleeding ceased, operation was carried out.

The patient had also received continuous medication with phenobarbital and penicillin. With the exception of a few days, morphine sulfate, 10 mg., was given every 8 hours. Mersalyl, 1 ml.,

was given thrice weekly, in the interval between the second and third major bouts of bleeding. Although attended by moderate increases in the urinary output, the drug did not prevent the third and fourth episodes of hemoptysis. There was no evidence of abnormal breakdown of transfused blood cells.

At operation the pulmonary artery was large and tense, measuring 4 cm. in diameter. The mean pulmonary artery pressure was estimated at 65 mm. Hg. The left atrium was also enlarged and tense and the pressure therein was in excess of 35 mm. Hg. The mitral diaphragm was elastic and the stenosis extreme, measuring 0.5 cm. in its greater diameter. Both commissures were split by finger and knife to the atrioventricular ring. The final opening was 3 cm. across; no incompetence resulted. There was a systolic thrill over the base of the aorta but this was slight and not thought to indicate functionally important aortic valvular disease. The left atrial pressure fell to a normal level while that in the main pulmonary artery reached approximately 35 mm. Hg.

Postoperative progress was uneventful. There was no further hemoptysis apart from some dark red staining of the sputum on the first day. Immediately after the operation, the blood pressure was 120/55 mm. Hg. and the diastolic pressure rose progressively to 65 to 70 mm. Hg. The patient was kept in the hospital for 5½ weeks after operation. Antenatal care was also uneventful. She was admitted for 2 weeks of bed rest in the eighth month and again some 2 weeks before the expected time of delivery. At full term she was delivered of a healthy infant weighing 6 lb. 15 oz. Labor was normal, the first stage lasted 12 hours 45 minutes and the second stage 25 minutes.

Following delivery the patient's condition was excellent and she was allowed home after 9 days. When seen 5 months later she was well, without cardiac disability and there had been no further hemoptysis. The lung fields remained clear (fig. 4).

Histologic examination of the tip of the lingula of the left lung indicated that the pulmonary arterioles showed minimal intimal thickening with some reduplication of the internal elastic lamina and medial hypertrophy with moderate sclerotic changes; the lumen-to-wall ratio was 2.9/1. Moderate pericapillary fibrosis existed while the pulmonary veins were the site of muscular hypertrophy.

DISCUSSION

Hemoptysis in mitral stenosis is often a feature of the earlier phases of the clinical course, at a time when breathlessness on exertion may not be great and when dyspnea

at rest and congestive cardiac failure are absent. Such was the situation in this case. Some hold the view that this form of pulmonary bleeding is venous, coming from the bronchial veins or pulmonary-bronchial venous anastomoses.² The frankly red blood in this case was in keeping with hemorrhage from the venous side of the pulmonary circulation. According to Wood,¹ sudden profuse hemoptysis in mitral stenosis is due to sudden rise in pulmonary venous pressure and may be regarded as "a safety valve, and is inevitably self-limiting, ceasing when the pulmonary venous pressure has fallen sufficiently." In his experience pulmonary apoplexy in mitral stenosis is not a serious symptom and has never proved fatal. Thompson and Stewart³ found that the amount of blood coughed up had no prognostic significance, and this form of pulmonary hemorrhage was never a serious threat to life. With particular reference to their experience of mitral stenosis in pregnancy, Marquis⁴ and Muleahy⁵ have not had to recommend operative intervention because of hemoptysis.

It was in recognition of the good immediate prognosis in such hemoptysis that the initial conservative management of this case was instituted and continued. The time came, however, when continuance of this regime seemed to carry a greater risk to life than surgical intervention. The gratifying outcome of this single case obviously does not prove the correctness of the decision made when considered out of context. On the other hand it was expected that as soon as the obstruction at the mitral valve had been relieved, the tendency to hemoptysis would diminish or disappear.

Several factors may have contributed to the severity of the bleeding. The main ones appear to have been pregnancy and the collapse of the right lung. While hemoptysis had occurred during the previous 3 years, it had never reached the frequency and profusion attained during the fourth and fifth months of pregnancy. At this time it is well known that increased blood volume and cardiac output are becoming established. These

in turn will tend to cause a rise in pressure in the pulmonary circulation in the presence of mitral stenosis.

Collapse of the right lung presumably resulted from aspiration of blood into the bronchial tree. It is likely that the source of the first hemorrhage was also on the right side. It is not known whether subsequent bleeding came from the same or from the opposite side or from both. It would seem possible, however, that the severity of the bleeding may in some way have been aggravated by the collapse of the lung, since the more massive hemorrhages occurred during this period and were less severe when the right lung had regained aeration and function. During the period of collapse blood would have been diverted away from the airless lung to augment the flow to the left lung bed, thereby increasing the pressure in the left pulmonary circulation. Again, within the collapsed lung itself, altered pressure relations, particularly between the air passages and the pulmonary veins may have contributed to the unusual severity of the hemorrhages.

Later in pregnancy deficiency of fibrinogen might conceivably be an aggravating cause of such pulmonary bleeding. In the present case there was no abnormality of blood clotting.

SUMMARY

A case is presented in which mitral commissurotomy was performed in the fifth month of pregnancy because of recurrent profuse

hemoptysis. After relief of tight mitral stenosis, hemoptysis ceased. Pregnancy continued to term without complication and a normal healthy child was delivered.

Some points relevant to hemoptysis in mitral stenosis complicating pregnancy are discussed.

ACKNOWLEDGMENT

We are grateful to Professor Stanley Alstead for permission to publish this case and to Drs. A. S. Rogen, J. G. Macarthur and H. R. L. Fraser for their advice in consultation.

SUMMARY IN INTERLINGUA

Es presentate un caso in que commissurotomia mitral esseva executate in le quinte mense de pregnantia a causa de recurrente e profuse hemoptysis. Post le alleviamento del stricte stenosis mitral, le hemoptysis cessava. Le pregnantia continuava sin complication, e un infante normal nasceva a termino.

Es discutite certe aspectos de hemoptysis in stenosis mitral como complication de pregnantias.

REFERENCES

1. WOOD, P.: An appreciation of mitral stenosis. *Brit. M. J.* 1: 1051, 1954.
2. GILROY, J. C., MARCHAND, P., AND WILSON, V. H.: The role of the bronchial veins in mitral stenosis. *Lancet* 2: 957, 1952.
3. THOMPSON, A. C., AND STEWART, W. C.: Hemoptysis in mitral stenosis. *J.A.M.A.* 147: 21, 1951.
4. MARQUIS, R. M.: Personal communication, 1957.
5. MULCAHY, R.: Personal communication, 1957.



Interrelationship of Drugs Influencing Arterial Pressure in Man

By WALTER REDISCH, M.D., FRANCISCO F. TANGCO, M.D., ARTHUR J. LEWIS, M.D., MARIA AURORA ANTONIO, M.D., KURT DECRINIS, M.D., AND J. MURRAY STEELE, M.D.

With the technical assistance of Dorothy Andrews and Stephen Menkes

Comparison of hemodynamic changes (cardiac output, renal plasma flow, and extremity blood flow) observed during reserpine-induced hypotension with those occurring during pentolinium-induced hypotension suggests better adaptation following reserpine. This difference is believed to be related to the gradation of onset of hypotension. It was found that reserpine-induced hypotension is potentiated by norepinephrine, and pentolinium-induced hypotension by serotonin. Pretreatment with the hypotensive agent increased the pressor response to norepinephrine and serotonin respectively, if the pressor substance was administered before the onset of hypotension.

THE mechanism of action of pressor and depressor substances and their interrelationship have been of considerable interest to all workers concerned with the study of hypertensive disease. In this paper some studies are reported concerning relationships between reserpine (Serpasil), pentolinium (Ansolsen), norepinephrine, and serotonin. First, responses to 2 different hypotensive agents, namely pentolinium tartrate (Ansolsen) and reserpine (Serpasil) were compared with each other and correlated with the clinical behavior of the subjects in whom hypotension was induced. Then pressure responses to serotonin were studied. Finally, the behavior of pressure responses to norepinephrine and serotonin were ascertained after pretreatment with each of the 2 hypotensive agents, pentolinium and reserpine, before and after the hypotensive effect had become manifest.

METHODS AND MATERIAL

The response of hypertensive and normotensive

From the Research Service (Third New York University) Medical Division, Goldwater Memorial Hospital, and the Department of Medicine, New York University College of Medicine, New York, N. Y.

This work was aided by a grant from the National Heart Institute, National Institutes of Health, Bethesda, Md.

Drs. Tangeo and Lewis are fellows of the New York Heart Association.

subjects was studied in 74 experiments. Physiologic measurements of peripheral vascular beds were done by venous occlusion plethysmography, by means of apparatus previously described.¹ Plasma flow through a visceral (renal) vascular bed was measured with the para-aminohippurate infusion method.² Cardiac output was estimated from an arterial dilution curve after rapid injection of Na^{24} by the method described by Powers,³ with minor modifications. Whenever these measurements were carried out, the subject was tested under basal conditions in a constant temperature room at 20 C. and 55 per cent humidity, as described previously.⁴ Whenever only the responses of arterial pressure, heart rate, and clinical behavior were ascertained, the experiments were performed under ward conditions. Three drugs were given in single intravenous doses: reserpine (Serpasil) 3 mg., pentolinium (Ansolsen) 3.5 mg., serotonin 2.5 mg. Norepinephrine was used in a solution of 4 mg. in 1000 ml. of 5 per cent glucose in water at an infusion rate of 20 drops per minute.

RESULTS

Single intravenous injections of 3.0 mg. of reserpine were given to 17 patients with essential hypertension in 38 experiments. In 36 of these, there was a marked drop in both systolic and diastolic pressures. The drop took place in a characteristic gradual fashion, reaching a maximum after 1½ to 5 hours. The total duration of pressure response was from several hours to 5 days.

By contrast, after intravenous injection of a ganglionic-blocking agent, in this case 3.5

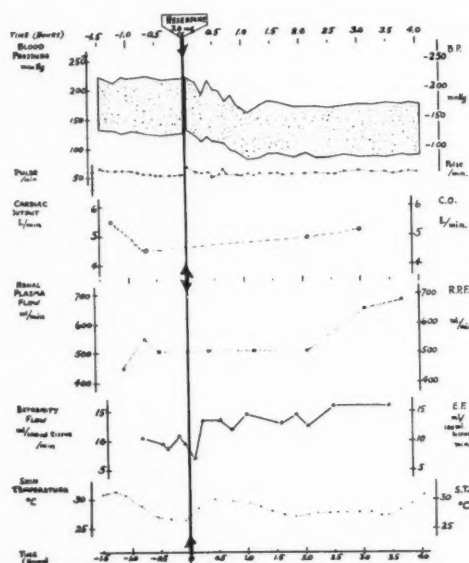


FIG. 1. Changes in arterial pressure, pulse rate, cardiac output, renal plasma flow, blood flow to the lower extremity, and surface temperature of the great toe following intravenous administration of reserpine.

mg. of pentolinium (11 experiments), there was an immediate drop in both systolic and diastolic pressures with return of diastolic pressure to pre-experimental levels within $\frac{1}{2}$ to 3 hours, while the return of systolic pressure required several hours.

The hypotensive response to reserpine was regularly associated with an early short-lasting increase in blood flow to the lower extremities, an equally brief but delayed increase in renal plasma flow, and no measurable change in cardiac output. The pulse rate remained unchanged or was slightly increased (fig. 1). In contrast is the hypotension following ganglionic blocking, which is associated with diminished cardiac output, a marked increase in blood flow to the extremities, and marked decrease in renal plasma flow. The known side effects associated with the precipitous fall in arterial pressure after administration of ganglionic-blocking agents are noticeably absent after reserpine. There was no postural hypotension or other clinical side effects, except mild flushing. Infusion of norepinephrine restored promptly the lev-

els of both systolic and diastolic arterial pressure lowered by reserpine. When norepinephrine was infused after the hypotensive action of reserpine had set in (9 experiments) there was immediate rise in pressure. When the infusion was discontinued, pressures returned to the former hypotensive levels produced by reserpine and then dropped to even lower levels that were maintained for many hours (fig. 2).

Recently, attention has been focused on 5-hydroxy-tryptamine, commonly called serotonin. This substance, as Brodie and his co-workers⁵ have shown, has a peculiar relationship to reserpine. It is stored predominantly in intestines, brain, and platelets and, when released into the blood stream, it is rapidly destroyed by amine oxidase. Reserpine causes depletion of serotonin depots that outlasts the presence of reserpine in the serum. This point is of particular interest, because the hypotensive effect of a single dose of reserpine also outlasts the presence of the drug in the serum.⁶

Serotonin, in doses of 2.5 mg., was administered intravenously in 14 experiments and was found regularly to increase both systolic and diastolic pressures. The rise was immediate (within 2 to 10 minutes) followed by a short-lasting drop in both levels of pressure (fig. 3). There was no essential change in response to the injection of serotonin during the maximal hypotension induced by intravenous injection of 3.0 mg. of reserpine in any of 7 experiments. When serotonin was injected 10 minutes after reserpine, however, before the onset of the hypotensive response, the blood pressure rose markedly, but the following hypotensive response to reserpine seemed unaltered.

In contrast, when 2.5 mg. of serotonin were injected during pentolinium-induced hypotension, there was a short elevation followed by a marked and sustained drop in both systolic and diastolic pressures exceeding considerably the hypotensive effect of pentolinium alone in all of 7 experiments (fig. 4). When 2.5 mg. of serotonin were injected immediately following 3.5 mg. of pentolinium,

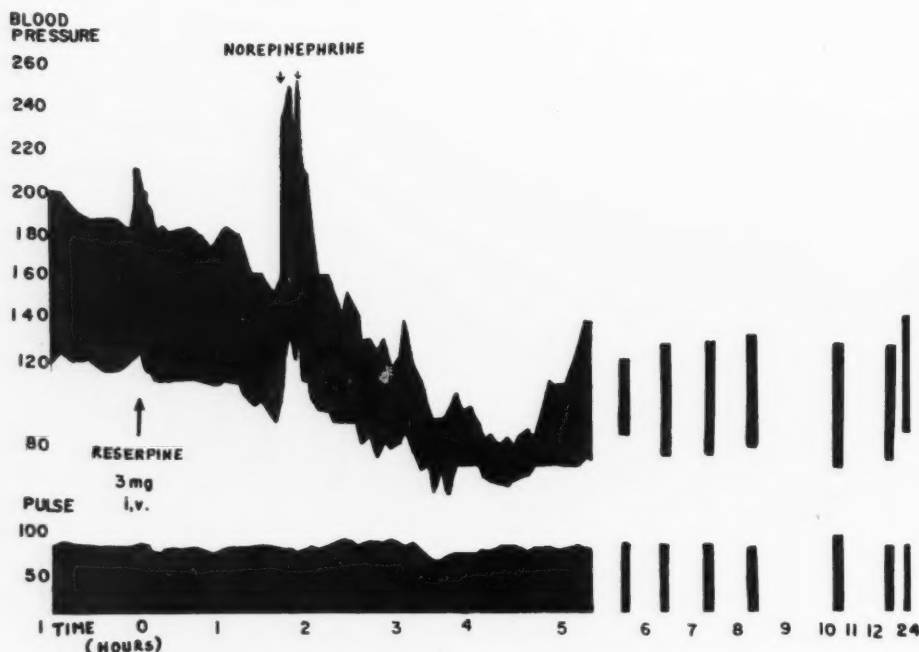


Fig. 2. Arterial pressure curve following the infusion of norepinephrine during reserpine-induced hypotension.

there was a marked rise in arterial pressure followed by the expected hypotensive phase.

Studies carried out in normotensive subjects showed essentially the same directional responses as in hypertensives, but of considerably lesser magnitude.

DISCUSSION

During the hypotensive response to reserpine the pressor effects of norepinephrine remain unimpaired. The type of response in arterial pressure to intravenous administration of reserpine is distinctly different from that following ganglionic blockers. The paucity of changes in cardiac output and in blood flow through the visceral and peripheral beds studied, together with the absence of severe clinical side effects, suggests strongly that the slow decrease in arterial pressure following reserpine permits hemodynamic adaptation that may not be possible during the precipitous fall of pressure in response to ganglionic blocking agents.

Epinephrine and norepinephrine have no effect upon pressure in the presence of adrenergic agents or when adrenergic blockade has been achieved. However, when arterial pressure has been lowered by a ganglionic blocking agent, the ability of epinephrine and norepinephrine to elevate pressures remains unimpaired. The same proved true in reserpine-induced hypotension. However, after discontinuation of norepinephrine infusion, the arterial pressure dropped to even lower levels than before. Even under these circumstances, the patients did not experience any distressing side effects, although they became sleepy and felt "weak."

There is some discrepancy in the reports on effects of serotonin upon arterial pressure in man. It has been described by various workers as hypertensive (Spies and Stone, dose: 0.5 to 5.0 mg.);⁷ hypotensive (Page and McCubbin, dose: 0.06 to 0.12 mg.);⁸ and biphasic (Page and McCubbin, dose: 0.3 to 1.8 mg.).⁹ Ersparmer,¹⁰ who summarized the

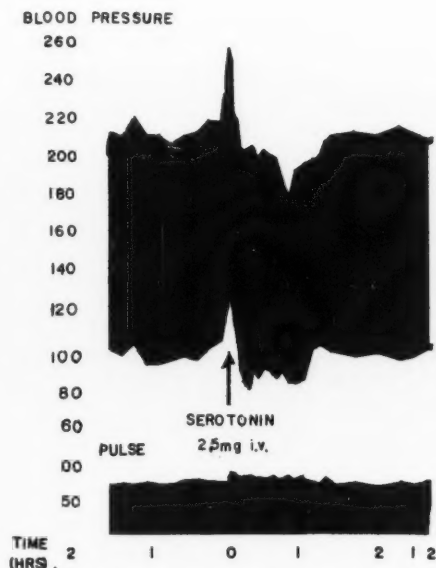


FIG. 3. Arterial pressure response to intravenous administration of serotonin.

findings, stated, "5-HT (serotonin) is neither a pure hypertensive nor a pure hypotensive agent. According to the dose, the route of administration, the anesthetic used, the neurogenic vascular tone, the general conditions of the cardiovascular apparatus and, above all, the animal species, 5-HT can elicit hypotensive, hypertensive and mixed responses." This statement refers to animal experiments as well as to those in man. The biphasic responses were described as a "fall, followed by a slight rise."

Hollander and Michelson¹¹ and Wilkins¹² reported that 0.3 to 1.5 mg. usually caused a hypertensive effect, with or without antecedent decrease in pressure. This effect was not prevented by hexamethonium, phentolamine (Regitine), atropine, and antihistaminic drugs.

In our experience serotonin in single intravenous doses of 2.5 mg. acts essentially as a pressor agent; usually this fast and fleeting action was followed by a slight but distinct depressor effect. This observation seems the more surprising, since it has been pointed out¹³ that "the levels of blood pressure in

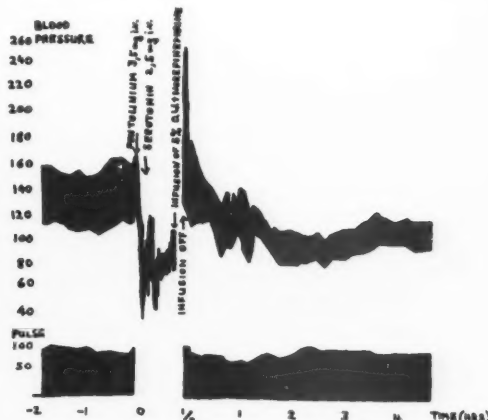


FIG. 4. Arterial pressure curve following the intravenous injection of serotonin during pentolinium-induced hypotension and after (emergency) infusion of norepinephrine.

carcinoid patients are not consistent with the concept that serotonin is a pressor substance in man."

When serotonin was injected soon after reserpine, its pressor action seemed enhanced, but when it was given at maximal hypotension, its effect was the same as without reserpine. Pentolinium did not influence the pressor action of serotonin.

Serotonin did not exert any influence on reserpine-induced hypotension. When serotonin was given immediately following pentolinium, it did not influence the hypotensive effect, but when given at maximal hypotension, it markedly potentiated this phase. The observation is of interest that change in timing without change in dosage produces marked differences in the effects of depressor and pressor substances administered in sequence. It suggests that one is dealing, not simply with pharmacologic potentiation, but rather with alterations in pressure-regulating mechanisms.

SUMMARY

Observations on the hemodynamic changes accompanying reserpine-induced hypotension are reported and compared with those associated with pentolinium-induced hypotension.

It is suggested that the gradual onset of hypotension following reserpine permits hemodynamic adaptation.

Norepinephrine, given at maximal reserpine-induced hypotension, and serotonin, given at maximal pentolinium-induced hypotension, appear to potentiate the hypotensive state markedly. When the pressor substances were given before the onset of hypotension, no such effect was observed, but there seemed to be an increased pressor response.

SUMMARY IN INTERLINGUA

Observationes del alterationes hemodynamic in hypotension inducite per reserpina es reportate e comparate con observationes correspondente in hypotension inducite per pentolinium. Es formulate le these que le emergentia gradual del hypotension a reserpina permitte un adaptation hemodynamic.

Le administration de norepinephrina in stato de hypotension maximal post reserpina e de serotonina in stato de hypotension maximal post pentolinium es apparentemente capace a potentiar le hypotensivitate a grados considerable. Quando le substantias pressori esseva administrate ante le declaration del stato hypotensive, nulle tal effecto esseva notate, sed il pareva occurrer un augmento del responsa pressori.

REFERENCES

1. REDISCH, W., WERTHEIMER, L., DELISLE, C., AND STEELE, J. M.: Comparison of various vascular beds in man; their responses to a simple vasodilator stimulus. *Circulation* **9**: 63, 1954.
2. BERGER, E. Y., FARRER, S. J., AND EARLE, D. P., JR.: Comparison of the constant infusion and urine collection methods for the measurement of renal function. *J. Clin. Invest.* **27**: 710, 1948.
3. POWERS, S. R., ROSSI, H. H., AND PAPPER, E. M.: An instrument for measurement of cardiac output. *Rev. Scient. Instruments* **23**: 178, 1952.
4. REDISCH, W., SHECKMAN, E., AND STEELE, J. M.: Skin temperature responses of normal human subjects to various conditions. *Circulation* **6**: 862, 1952.
5. PLETSCHER, A., SHORE, T. A., AND BRODIE, B. B.: Serotonin as a mediator of reserpine action in brain. *J. Pharm. & Exper. Therap.* **116**: 84, 1956.
6. REDISCH, W., TANGCO, F. F., LEWIS, A. J., AND STEELE, J. M.: Vasomotor responses to reserpine and pressor responses to serotonin in man. 20th International Congress of Physiology. Paper No. 751, Brussels, Belgium, August 4, 1956.
7. SPIES, T. D., AND STONE, R. E.: Effect of serotonin on blood pressure and lack of effect of antimetabolite. *J.A.M.A.* **150**: 1599, 1952.
8. PAGE, I. H., AND McCUBBIN, J. W.: The variable arterial pressure response to serotonin in laboratory animals and man. *Circulation* **1**: 354, 1953.
9. PAGE, I. H.: Serotonin (5-Hydroxytryptamine). *Physiol. Rev.* **34**: 563, 1954.
10. ERSPAMER, V.: Pharmacology of indolealkylamines. *Pharmacol. Rev.* **6**: 425, 1954.
11. HOLLANDER, W., AND MICHELSON, A. L.: The effects of serotonin and antiserotonin in hypertensive man. *J. Clin. Invest.* **35**: 712, 1956.
12. WILKINS, R. W.: Serotonin, antiserotonin and hypertension. *New England J. Med.* **255**: 115, 1956.
13. MATTINGLY, T. W., AND SJOERDSMA, A.: The cardiovascular manifestations of functioning carcinoid tumors. *Mod. Concepts Cardiovas. Dis.* **25**: 337, 1956.



Left Atrial Electrokymography in Mitral Insufficiency in Man

A Correlative Study by Angiocardiography and Left Heart Catheterization

By RICHARD D. JUDGE, M.D., MELVIN M. FIGLEY, M.D., AND HERBERT E. SLOAN, M.D.

The relationship of the left atrial border movements to underlying pressure and volume changes was investigated in individual human subjects with proved mitral insufficiency. Based on these observations, criteria for the recognition of hemodynamically significant mitral insufficiency have been revised. Special emphasis is placed on a rapid inward movement of the atrial wall during the period of early diastolic emptying. Application of these criteria to a group of patients with surgically proved valvular lesions suggests that they are more reliable than those previously described.

THE development of the electrokymograph by Henny and co-workers¹ was followed shortly by its application to the study of left atrial border movements in mitral valve disease.² Certain criteria were established on the basis of clinical correlations and theoretical considerations for the recognition of mitral insufficiency. Subsequent study of normal subjects,³ however, as well as correlations with surgical observations,⁴ cast some doubt on the reliability of these criteria. As a result, the electrokymograph has been generally supplanted by other diagnostic methods for the detection of mitral insufficiency.

The complex origin of the records that represent movements of the left atrial border makes their interpretation difficult. Not only may they represent displacement, rotation, and volume change, but, due to the central position of the chamber, they may theoretically be altered by superimposed variations of density of the pulmonary vasculature or aorta, depending upon the projection. No study to date has comprehensively investigated the basic relationship of these border

movements to underlying pressure and volume changes in individual human subjects. Frequent reference is made to the studies of Wiggers and Feil⁵ on acute, experimental mitral insufficiency in dogs, which correlated left atrial pressure and volume changes. Andersson⁶ described similarities between left atrial pressure and electrokymographic curves in 2 patients. Recently these curves have been studied in experimental mitral insufficiency in dogs in our laboratory.⁷ The application of electrokymography, angiocardiography, and left heart catheterization to patients undergoing mitral valve surgery now allows a more accurate documentation of these interrelationships in man.

With these considerations in mind, we have undertaken a reappraisal of the electrokymographic criteria for mitral insufficiency by correlating left atrial border movements with atrial volume variations as determined by angiocardiography, and with pressure curves obtained by left atrial puncture. In the interest of completeness, the original electrokymograms in experimental mitral insufficiency⁷ have been critically re-evaluated. On the basis of criteria established by these observations, left atrial electrokymograms from a group of 44 patients who ultimately underwent mitral surgery were evaluated for evidence of mitral insufficiency.

From the Departments of Medicine, Radiology and Surgery, University of Michigan, Ann Arbor, Mich.

Supported by the John and Mary R. Markle Fund and by a grant from the Michigan Heart Association.

METHODS

Electrokymographic tracings were made with the patient sitting erect, with breathing suspended in midinspiration. Recordings were made in the frontal position over the left atrial appendage and, when possible, over the right border of the left atrium. Right and left anterior oblique and lateral projections were also used to record atrial movements, both directly and from the adjacent barium-filled esophagus. Most records were obtained with a Cambridge* electrokymograph coupled to a Cambridge Simplitrol string galvanometer, with a simultaneous phonocardiogram and carotid sphygmogram. More recently an Elema† dual phototube electrokymograph system and Mingograff‡ jet writer have been used with electrocardiographic timing. Film and paper speeds of 50 mm. per second were routinely employed.

Angiocardiography was carried out by rapid, manual injection of 50 ml. of 70 per cent sodium acetate (Urokon‡) in the antecubital vein, with the patient sitting in the posteroanterior, left posterior oblique, or left lateral projection, at a target film distance of 36 inches. Exposures of 1/15 or 1/10 second were obtained at rates of 1.3 or 2 per second, and registered on a simultaneous electrocardiogram. The patient was instructed to hold his breath in full inspiration during the anticipated period of left heart opacification. Films were selected where the left atrial border was sharply demarcated in its entirety, and its outline was pencilled to facilitate measurement of the area (fig. 1). As a rule the atrial margins were quite sharp, except during atrial systole, despite the relatively long exposures. The atrial appendage, however, had to be excluded because of indistinct outline, and arbitrary straight lines were drawn across the base of the pulmonary veins. The average of 2 measurements of the area obtained with a polar planimeter (seldom differing as much as 1 cm.²) was plotted against the exposure instant in the cardiac cycle. In this way a curve of the relative cyclic variations of the left atrial area was obtained. In 2 patients curves were obtained in both frontal and lateral projection. Since these had almost identical shapes, it was assumed that a single area curve was representative of variations of relative atrial volume. Corrections for image magnification, necessarily different for each patient, were not made, since our interest lay only in relative variations.

Left atrial pressure records were obtained by transthoracic puncture with a thin-walled 18-gage

needle as described by Björk and associates.⁴ Pressures were recorded directly from the needle with a Statham pressure transducer (P23G)* and a modified Grass† electroencephalographic direct writer.

In evaluating the electrokymographic tracings from candidates for valvulotomy, the criteria developed from the studies mentioned were applied without knowledge of name, clinical findings, or surgical findings. Patients were graded into 2 categories: no insufficiency or insignificant insufficiency, and predominant, clinically significant insufficiency. The latter diagnosis was decided on if typical patterns were clearly identified.

Critique

Most of the factors that are likely to cause electrokymographic records to be unsatisfactory or erroneously interpreted in mitral disease can be recognized. They can be separated into the following categories:

1. Failure to obtain representative tracings due to: inability of the patient to cooperate by sitting immobile and suspending respirations; pleural or pericardial effusions; obscure left atrial borders (usually due to massive cardiac enlargement); rapid or very irregular rhythm; and inaccurate position of the slit.
2. Failure of the electrokymogram to reflect the underlying physiologic changes due to: a large left atrial clot; and giant atrial size or other factors (calcification, fibrosis) resulting in rigidity of the wall.
3. Additional hemodynamic abnormalities that alter the pattern, such as aortic valve disease and congestive failure.
4. Lack of quantitation of the pulse amplitude. Without a method of standardization, considerable distortion can be introduced via indiscriminate manipulation of the amplifier gain. If the amplitude of the deflections could be measured in absolute units, calculation of the slope of the various emptying curves could be expected to improve the reliability of the method. This problem is under consideration.

In spite of these drawbacks, the electrokymogram has certain advantages. It is simple. It can be performed by a single person in 20 to 30 minutes following routine fluoroscopy. It carries no hazard for the patient. It causes no discomfort. With an understanding of the underlying hemodynamics reflected by the electrokymographic pattern, its interpretation may be placed on a more rational and reliable basis than previously. Left atrial (and ventricular) puncture may then be necessary only in very select cases.

*Cambridge Instrument Co., Ossining, N. Y.

†Elema-Järnhus AB, Stockholm, Sweden.

‡Mallinckrodt Chemical Works, St. Louis, Mo.

*Statham Laboratories Inc., Los Angeles, Cal.

†Grass Instrument Co., Quincy, Mass.

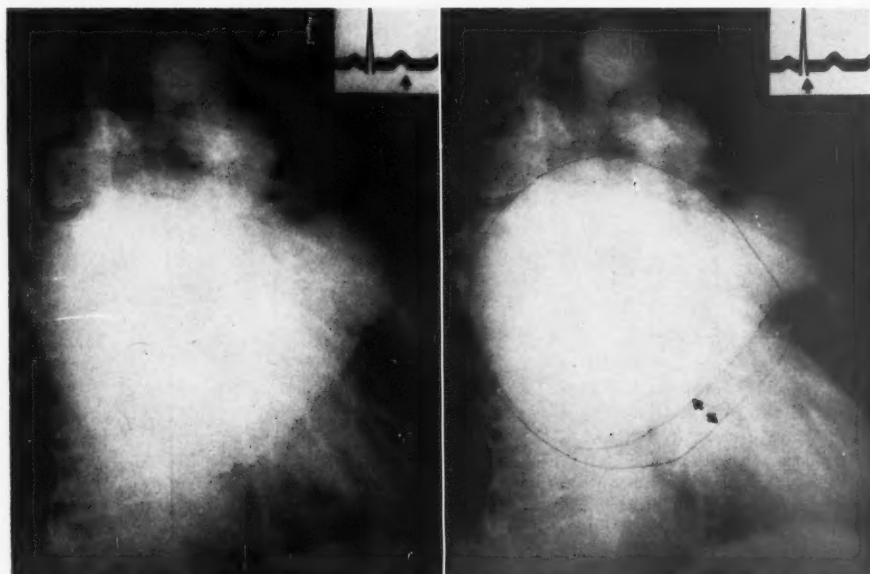


Fig. 1. Angiocardiogram, left posterior oblique projection, of a patient with mitral insufficiency. Extremes of left atrial size are shown. The variation is the largest encountered in any patient and is plotted in figure 2, patient LR.

At simple venous angiocardigraphy the circulation of contrast material through the heart is sufficiently prolonged by mitral valve disease so that filming rates of 1 to 2 per second will provide 8 to 10 films showing a well-opacified left atrium. These are generally, although not always, scattered in random fashion throughout the heart cycle. If their position in the cycle is known through a timing device, one can measure diameter, circumference, or area of the left atrium, and gain some idea of the relative cyclic volume variations.

The method has distinct limitations, and even under fortunate circumstances supplies only a minimum of points for plotting a curve; (ideally, 15 to 20 films in 2 planes at right angles in a single cardiac cycle with some mechanical event for timing would be desirable). The method used requires that the heart rate be regular but asynchronous with the filming rate. Respiration must be suspended to prevent motion. In some instances, through an unintentional Valsalva effect, there may be progressive reduction of venous return so that diastolic filling of the atrium is not uniform for each cycle. A number of circumstances may invalidate the method: rapid circulation as in the normal; atrial fibrillation with an irregular ventricular rate (found more often than not in serious mitral disease); synchronous heart and filming rates; uncontrolled respiration; unsuccessful timing; poor angiocardigraphic technique resulting in

indistinct atrial margins. Due to 1 or more of these factors, satisfactory curves could be drawn for only 11 of 45 patients with mitral disease studied. Surgical exploration was performed in 9 of these and disclosed high-grade stenosis in 5 and predominant insufficiency in 4.

OBSERVATIONS AND RESULTS

Relation of Left Atrial Border Movements to Volume Variations

The left atrial volume variations in mitral valve disease follow simple curves with minima occurring at or slightly after the Q wave and maxima at about the end of the T wave (fig. 2). A more accurate statement cannot be made because of insufficient observations at the critical points, but the basic patterns are consistent. They correlate well with the mechanical events known to occur at these times,⁹ and with other angiocardigraphic observations.¹⁰

The ascending or filling limb of the curve is steep in both stenosis and insufficiency and would not allow their differentiation based on its form alone, according to our very limited observations (fig. 2). The descending or

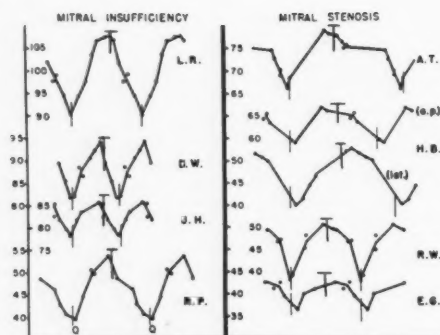


FIG. 2. Cyclic variations in left atrial area in surgically proved patients with either dominant mitral stenosis or insufficiency. Scale is square centimeters. Vertical lines, Q wave; crossed lines, end of T wave. Contradicting measurements at the same time are averaged. Slight irregularities on both ascending and descending limbs might be plotted in some curves, but this is doubtfully permissible within the accuracy of the method.

emptying limb, however, has distinctive patterns. In mitral insufficiency emptying is rapid and quite complete shortly after its inception. In all but 1 instance the chamber emptied faster than it filled. This emptying pattern is to be expected, for, as will be seen, the pressure gradient is high at this time and there is no mechanical impediment to flow. It is reassuring to find a very similar curve in the pioneering studies on mitral insufficiency by Wiggers and Feil.⁵ Our tracings, however, lack the secondary distention of the atrium late in ventricular diastole, as shown in their curve.

The emptying pattern is quite different in mitral stenosis. Some emptying occurs early in ventricular diastole, but most of it occurs later with atrial systole. The curve has a decided middiastolic convexity or plateau, for the mechanical obstruction to flow interferes with atrial decompression. During early diastole flow probably depends mainly upon maintenance of the pressure gradient by the elasticity of the left atrium and pulmonary veins. A more rapid decrease in volume then occurs with additional compression incident to atrial systole. (Since this work has been completed a similar independent angiocardio-

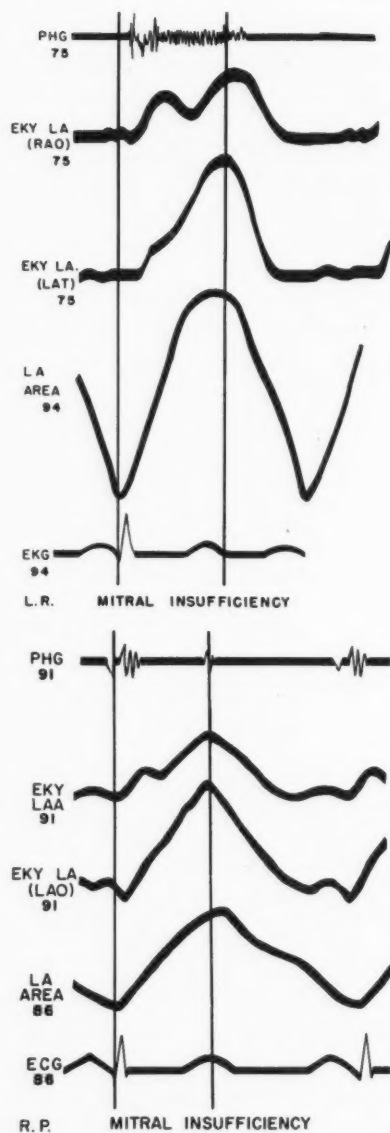


FIG. 3. Top. Patient L.R. Mitral insufficiency (surgically proved). Correlation of left atrial border movements (electrokymogram) and relative atrial volume (LA area). Heart rates, indicated on the left, are not identical. Bottom. Patient R.P. Mitral insufficiency (surgically proved). Correlation of left atrial border movements (electrokymogram) and relative atrial volume (LA area). Heart rates, indicated on the left, are nearly the same. Electrokymograms were recorded from the left atrial appendage (LAA) and left atrium (LA).

graphic determination of the relative volume variations of the left atrium in mitral disease has been published by Arvidsson and Odman.¹¹ More rapid filming simultaneously in 2 planes allowed the preparation of curves quite similar to those described above. The authors note the same features of the atrial emptying patterns and further suggest that the atrial filling curve may be somewhat steeper in mitral insufficiency. The amplitude of the relative volume variations was greater in insufficiency.)

In all 4 cases of mitral insufficiency the electrokymogram invariably showed an inward movement in early ventricular diastole. Its onset, shortly after the second heart sound, followed closely the maximal outward position. Comparison of curves in 2 cases shows great similarity between volume changes and border movements throughout ventricular diastole (fig. 3).

In mitral stenosis movements during ventricular diastole followed the volume curves also (fig. 4). The relatively prolonged inward movement of large amplitude, during atrial systole, as emphasized by Andersson,⁶ is quite distinctive.

The movement and volume curves are not always similar throughout ventricular systole, however. The electrokymogram often shows an inflection and sometimes a distinct downward deflection (inward atrial movement) during early ventricular systole in both mitral stenosis and insufficiency. There is no suggestion of comparable change in the volume curves. Yet, as we have said, our data in this period are inadequate. Nevertheless, this is the period for the atrium to fill from the pulmonary veins, so that no decrease in volume can be reasonably expected. This movement, then, is probably a matter of atrial displacement or change in shape, occurring in time with the descent of the atrioventricular ring, and obscuring a coincident increase in volume.

In addition to defining the qualitative resemblance of the atrial border movements to volume changes, angiocardiology also gives a clear indication of their relative magnitude.

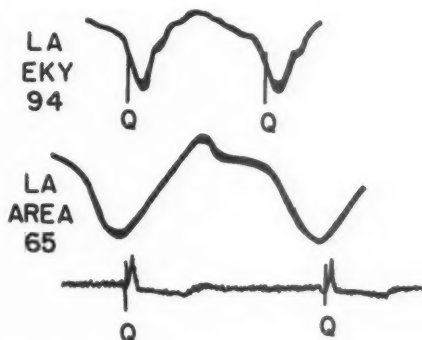


FIG. 4. Patient EM. Mitral stenosis (surgically proved). Correlation of left atrial border movements (electrokymogram) and atrial volume (LA area). Heart rates, indicated on the left, are widely divergent.

Figure 5 is representative of many experiences showing that the bulk of chamber-size variation is not necessarily reflected in surface movement. Wide oscillations of the atrioventricular rings allow reciprocal changes in atrial and ventricular volumes with relatively little surface movement.

Relation of Left Atrial Border Movements to Intracavitary Pressure Changes

A further understanding of the left atrial border movements in mitral valve disease has resulted from comparisons of the electrokymogram with the direct left atrial pressure tracing from the same patient. This has been possible in 11 cases to date. Nine of these were surgically verified, 5 showing predominant stenosis and 4 predominant insufficiency. Two were not operated on because of convincing evidence of predominant insufficiency. The electrokymographic pressure studies were not simultaneous, so that the conclusions that may be drawn from them must be limited. Furthermore, the electrokymographic studies were made with subjects erect with phonocardiographic timing, whereas pressure studies were made with subject prone with electrocardiographic timing. Despite these factors, an obvious qualitative similarity may be recognized in records from the same patient.

The form of the left atrial pressure tracing in experimental mitral insufficiency is well

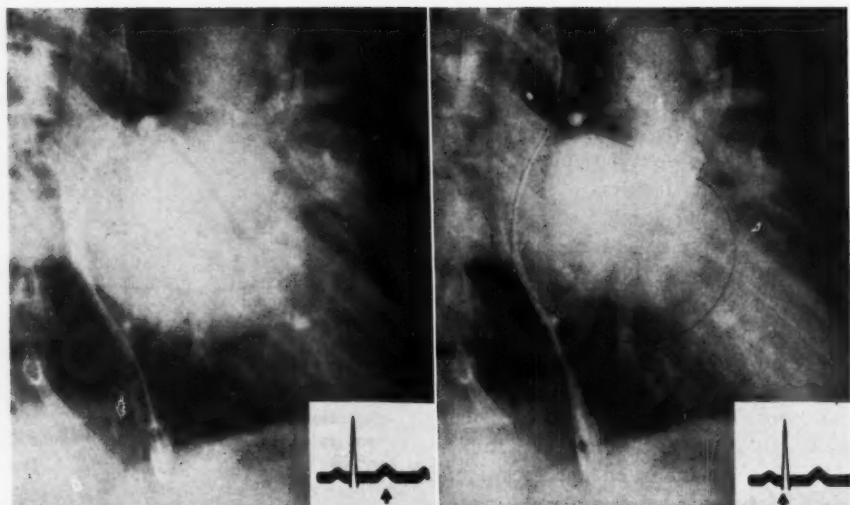


FIG. 5. Patient RW. Angiocardiogram, left posterior oblique projection, mitral stenosis. Extremes of size of the left atrium. Note the relatively slight positional change of the esophagus against the posterolateral atrial surface compared to the marked change in atrial size. Penciled lines on the right film indicate esophagus position and atrial margins of the left film.

established^{5, 12} and correlates with recently reported clinical records.^{13, 14} There is some reduction of the normal descent that follows the C wave in early ventricular systole, but the striking feature is the large, late systolic V wave (or so called regurgitant wave). The importance of a steep descent with rapid disappearance of a measurable gradient between left atrium and ventricle in early diastole has been stressed by Owen and Wood.¹⁵ Our records have shown these characteristic features in all instances of predominant insufficiency. From some cases of mitral stenosis with slight insufficiency we have obtained similar pressure curves, but there was the distinguishing feature of a diastolic gradient across the mitral valve in these patients.

There were similarities between the pressure record and the border movement tracings in all of our cases. With atrial fibrillation this was true throughout the entire cardiac cycle. Where a normal sinus mechanism prevailed, it was true except during atrial systole, when inward movement was accompanied by increased pressure. The form of the electrokymogram in surgically proved

cases of insufficiency had the same general outline as the pressure record. Figure 6 shows one example. Figure 7 shows 4 other cases demonstrating the similarity of the pressure-electrokymogram relationship. Thus, it would seem that the left atrial border movements qualitatively reflect variations in pressure except during atrial systole.

Electrokymographic Records in Experimental Mitral Insufficiency

The records of experimental studies carried out with Nordenström and co-workers⁷ were reviewed. In 3 dogs with chronic mitral insufficiency and considerable left atrial dilatation border movements were similar. The prominent inward movement noted preoperatively in early ventricular systole was partially or completely effaced. The curve became essentially a single, large wave, rising to a peak in late ventricular systole and falling more rapidly than it rose in early ventricular diastole. Inward movement during atrial systole was reduced in amplitude and, because of tachycardia, merged with the early diastolic descent. In the fourth animal with acute

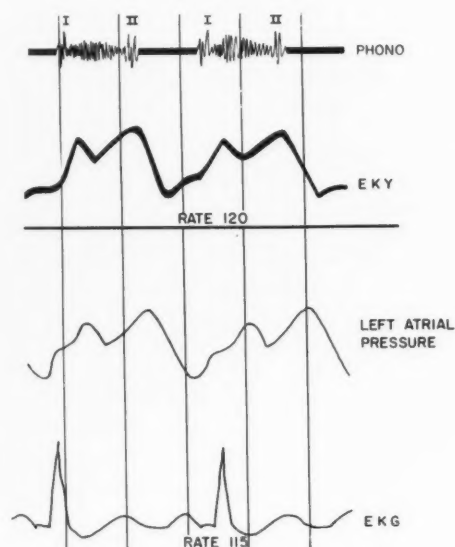


FIG. 6. Patient DW. Mitral insufficiency (surgically proved) Similarity of left atrial pressure curve and electrokymogram from the appendage is apparent. Pressure was 35/25 mm. Hg due to congestive failure. Rates were slightly different. Form of the electrokymogram is typical of insufficiency.

mitral regurgitation and with no recognizable left atrial dilatation, the only change was the appearance of a large positive wave in late ventricular systole.

Correlation between Surgical and Electroky-mographic Evidence of Mitral Insufficiency

On the basis of these observations, certain criteria were developed for the recognition of clinically significant mitral insufficiency by the left atrial electrokymogram (fig. 8). (A) A distinct and prominent outward (upward) movement in early systole synchronous with valve closure, succeeded by, (B) an inward (downward) movement, forming a trough of from 0.08 to 0.16 second duration in mid-systole, (C) a late systolic wave of greater amplitude than the initial peak with a gradual upward slope, (D) rapid collapse of this wave in early diastole, with return to baseline within 0.12 second, (E) complete or almost complete absence of inward (downward) movement due to atrial systole.

Electrokymograms from 44 patients who had surgical or pathologic verification of their lesions were evaluated without knowledge of

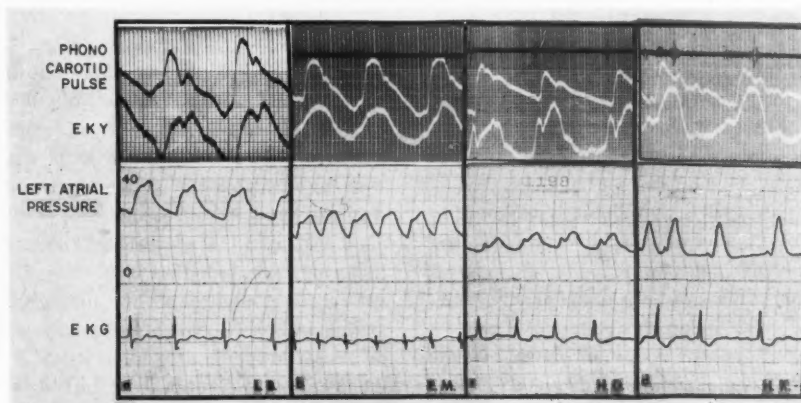


FIG. 7. Four examples showing the qualitative similarity between the left atrial pressure and the electrokymogram. Atrial fibrillation was present in all instances. Paper speeds for electrokymograms and pressure records were different. In A and B a small jet was discovered at surgery, but the predominant lesion was high grade stenosis. C and D were not subjected to surgery because of overwhelming evidence of insufficiency. From left to right the records show a pattern of progressively more insufficiency and less stenosis. In D is illustrated the type of curve expected in the most severe variety of mitral insufficiency.

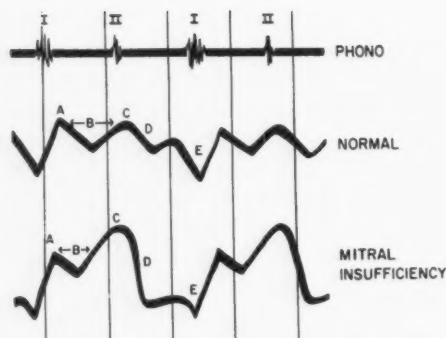


FIG. 8. Diagrammatic representation of a normal and insufficiency curve, showing features important in recognizing predominant mitral insufficiency by the electrokymogram. The rapid inward movement in early diastole in the lower curve, representing unimpeded atrial emptying, is of great diagnostic importance. Criteria include: An inflection, *A*, in early systole synchronous with valve closure. A deflection forming a trough, *B*, of from 0.08 to 0.16 second duration in midsystole. A late systolic wave, *C*, of greater amplitude than the initial peak, *A*. Rapid return of this wave to the baseline, *D*, within 0.12 second. Reduction in the duration and amplitude of the inward movement, *E*, due to atrial systole.

name, clinical data, or surgical findings. Wave patterns fulfilling the above criteria were searched for and, if clearly present in one or more projections, were considered indicative of significant mitral insufficiency. Patients were divided into 2 groups of absent or insignificant insufficiency and predominant insufficiency. The principal valvular lesion was correctly predicted in 9 cases of proved mitral insufficiency and in 33 cases of proved stenosis. Two patients with significant insufficiency failed to show a characteristic wave form in the available tracings (fig. 9).

Other observations of help in differentiating the basic valvular lesion can be made in retrospect. 1. With insufficiency of more severe degree deflections *A* and *B* (fig. 8) became smaller, while *C* and *D* increased in size. 2. With sinus rhythm the atrial systolic descent was broad and deep in severe mitral stenosis. 3. Border movements were of relatively greater amplitude with predominant insufficiency than with predominant stenosis. 4.

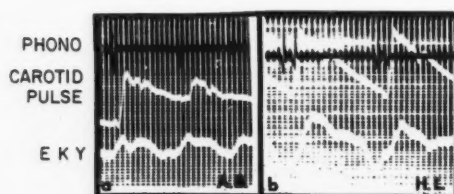


FIG. 9. Representative electrokymograms from 2 cases in which border movements failed to correlate with the surgical findings. *A*. Predominant mitral insufficiency: Electrocardiogram failed to show diagnostic pattern, despite the presence of atrial fibrillation. *B*. Aortic stenosis and insufficiency: Electrocardiogram suggested mitral stenosis (prominent inward movement present with atrial systole). Another patient with this combined lesion showed a similar pattern.

Atrial fibrillation tended to accentuate the electrokymographic signs of insufficiency.

DISCUSSION

"Systolic expansion" of the left atrium (apparent enlargement of the atrium during ventricular systole) with mitral regurgitation was first described clinically by Owen and Fenton in 1901¹⁶ and radiologically by Holzknecht¹⁷ in that same year. Its value as a sign of insufficiency has been repeatedly emphasized (most recently by Brigden and Leatham¹⁸). Elkin and associates,¹⁹ however, have reported this fluoroscopic finding in both stenosis and insufficiency. We believe that our angiocardigraphic and electrokymographic observations make it perfectly clear that to speak of "systolic expansion" of the left atrium with reference to the differentiation of mitral stenosis and insufficiency is meaningless. In either case (figs. 1-5), rapid filling of the atrium occurs during ventricular systole, whether from pulmonary veins alone or from the veins and left ventricle together. The difference lies not here, but in the manner of diastolic emptying, which is early and rapid with insufficiency, and prolonged and slow with stenosis. In our opinion the term "early diastolic collapse" would be more descriptive of the altered left atrial border movements in mitral insufficiency.

Early workers established criteria for normal atrial border movements²⁰⁻²⁴ and pointed to distortion of this pattern with the development of a "systolic plateau" in mitral regurgitation.²⁵⁻²⁸ The reliability of this sign was very quickly disputed, however, as a result of reports of plateau curves in normal subjects²⁹⁻³¹ and in cases of pure mitral stenosis.^{30, 32} Haring, Liu, and Trace³³ again emphasized a "plateau" contour of both the pressure and border movement records during ventricular systole, designating them "early," "intermediate," or "late," depending on their timing. There is no question that the contour of the left atrial electrokymogram changes during ventricular systole in both experimental and clinical mitral insufficiency. The normal descent during early ventricular ejection (fig. 8) may be distorted or effaced, and there is a definitely prominent upward movement throughout the last half of systole. But these changes are seldom of "plateau" configuration and of themselves are not distinctive. The rapid, early diastolic descent gives the curve its diagnostic contour. This inward movement is identical in time to the early diastolic decrease in left atrial volume, left atrial pressure (measured directly¹³ and indirectly,¹⁵) and esophageal pressure^{34, 35} in patients with surgically verified mitral insufficiency. Neither the volume nor the pressure changes in the left atrium are characterized by an abrupt prolonged systolic rise to a plateau. In our opinion, the accumulated evidence indicates that the descriptive term "systolic plateau" has no relation to underlying hemodynamic events and is therefore not a justifiable basis for the electrokymographic diagnosis of mitral insufficiency.

Based on the described observations, our concept of the relation of left atrial border movements to changes in volume and pressure can be stated simply. The movements during ventricular systole are qualitatively similar to pressure changes, while the diastolic movements are qualitatively similar to volume changes. The details in relation to mechanical events are as follows.

The initial outward movement during isometric contraction of the ventricle may be either positional or volumetric, for while the mitral valve is closed and thrust up into the floor of the atrium, the atrial volume has begun to increase by filling from the pulmonary veins. The recession that follows, coincident with rapid ventricular ejection and downward movement of the atrioventricular ring, is purely positional, for there is continued increase in the volume at this time. This recession is reduced or absent in mitral regurgitation. Our studies suggest that this change is most likely due to enlargement of the left atrium and distention of the pulmonary veins (features regularly present in mitral valvular disease) that might be expected to reduce their mobility without reducing the movements of the atrioventricular ring (figs. 1 and 2). In the experimental records a normal systolic recession was demonstrated only in the animal with acute insufficiency and no left atrial enlargement. This hypothesis provides explanation for the similarity of the systolic contour of the electrokymogram in mitral stenosis,⁶ where atrial dilatation is likewise present.

The atrial position in late ventricular systole and its movements during rapid ventricular filling and diastasis are qualitatively similar to both volume and pressure changes. This period, when the atrium passively reflects these phenomena, is the most important for the differentiation of mitral insufficiency and stenosis.

Atrial movements during atrial systole are qualitatively similar to changes in volume and are inversely related to pressure. Atrial emptying limited mainly to atrial systole is a feature of mitral stenosis (with normal sinus rhythm) and is not found in pure mitral insufficiency.

This simplified account of these relationships is much the same as that given in more detail by Andersson.⁶ It neglects the atrial surface used for recording and other seemingly minor influences, such as change in atrial shape or rotation. We claim no origi-

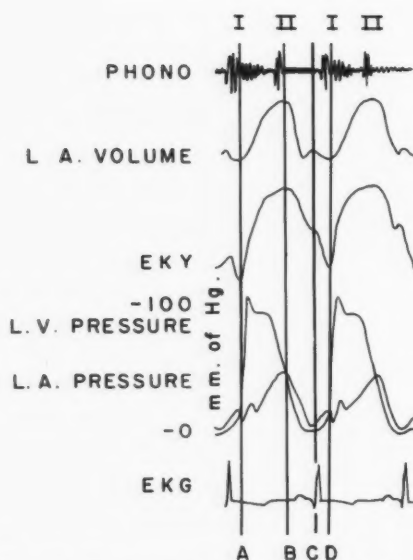


FIG. 10. Diagrammatic representation of the time relations of left heart pressures, left atrial volume, and border movement in mitral insufficiency. The electrocardiogram, pressures, and electrokymogram are traced from experimental records. The atrial volume and phonocardiogram are artificial. *AB* ventricular systole, *BC* early diastole emptying (passive), *CD* late diastolic emptying (atrial contraction).

nality for it but do provide some supporting hemodynamic measurements. An idealized diagram (fig. 10) based on synchronous pressure and electrokymographic records from 1 of the experimental animals illustrates these relationships in mitral insufficiency.

A cause of error in electrokymographic recognition of mitral insufficiency needs to be briefly mentioned. Two cases in whom this lesion was not detected had aortic stenosis and insufficiency with atrial movement curves suggesting mitral stenosis (fig. 9). It would seem reasonable that left ventricular hypertrophy or residual blood resulting from these lesions delayed the rapid inflow from the left atrium, upon which the recognition of mitral insufficiency depends. Thus, it is well to bear in mind the possibility that complicating lesions that impede left ventricular emptying (aortic valve lesions) may simulate mitral stenosis and obscure the recognition of mitral insufficiency.³⁶

It must also be clear that the inward movement in early ventricular diastole upon which we place emphasis does not specifically identify mitral insufficiency. It means simply that there is no impediment to left atrial emptying at this time. It occurs normally and it means mitral insufficiency only in established cases of mitral valve disease by excluding, with rare exception, significant mitral stenosis.

SUMMARY

Correlation of the left atrial electrokymogram with volume variations and pressure curves in experimental and clinical mitral insufficiency has resulted in a greater understanding of the basis for the changes observed in the border movements. The form of the electrokymogram in ventricular diastole appears to reflect primarily changes in the volume of this chamber. The pattern during ventricular systole seems to be a combination of slight changes in atrial position or shape superimposed on an expanding atrial volume. Based on these observations, criteria for the recognition of hemodynamically significant mitral insufficiency by the electrokymogram have been revised. Special emphasis is placed on a rapid inward movement of the atrial wall during the period of early diastolic emptying. Application of these criteria to a group of patients with surgically proved valvular lesions suggests that they are more reliable than those heretofore described.

ACKNOWLEDGMENT

We wish to express our gratitude to Dr. Franklin D. Johnston, Heart Station, University Hospital, Ann Arbor, Mich., and to Dr. Ulf Rudhe, Karolinska Sjukhuset, Stockholm, Sweden, for their encouragement and advice in the preparation of this work.

SUMMARY IN INTERLINGUA

Le correlation del electrokymogramma sinistro-atrial con variationes de volumine e curvas de pression in insuffientia mitral experimental e clinic ha resultate in un clarification del bases del alterationes observate in

le movimientos marginal. Le forma del electrokymogramma in diastole ventricular pare reflecter primariamente alterationes in le volumine de iste camera. In systole ventricular le conformation electrokymographic pare reflecter un combination de leve alterationes del position o del forma atrial superimponite a un volumine atrial in expansion. Super le base de iste observationes, le criterios pro le recognition electrokymographic de hemodynamicamente significative insufficiencia mitral ha essite reformulate. Attention special ha essite prestate al rapide movimento introrse del pariete atrial durante le periodo del vacuation diastolic initial. Le application de iste criterios a un gruppo de pacientes con chirurgicamente provate lesiones valvular pare indicar que illos es plus solide que le criterios describite in le passato.

REFERENCES

1. HENNY, G. C., BOONE, B. B., AND CHAMBERLAIN, W. E.: Electrocardiograph for recording heart motion, improved type. *Am. J. Roentgenol.* **57**: 409, 1947.
2. LUISADA, A. A., AND FLEISCHNER, F. G.: Dynamics of the left auricle in mitral valve lesions, fluorocardiographic study. *Am. J. Med.* **4**: 791, 1948.
3. SOLOFF, L. A., ZATUCHNI, J., AND STAUFFER, H. M.: The atrial border electrokymogram in mitral regurgitation. *Circulation* **6**: 96, 1952.
4. ABELMANN, W. H., ELLIS, L. B., AND HARKEN, D. E.: The diagnosis of mitral regurgitation: Evaluation of clinical criteria, fluoroscopy, phonocardiogram, auricular esophagram and electrokymogram. *Am. J. Med.* **15**: 5, 1953.
5. WIGGERS, C. J., AND FEIL, H.: The cardiodynamics of mitral insufficiency. *Heart* **9**: 149, 1922.
6. ANDERSSON, T.: Electrocardiographic examinations in mitral valve disease. *Acta radiol. Suppl.* **106**, Stockholm, 1953.
7. NORDENSTRÖM, B., STAMER, J. P., FIGLEY, M. M., AND SLOAN, H. E.: Selective roentgenographic contrast examination and electrokymography of the left heart in experimental mitral insufficiency. *Circulation* **15**: 682, 1957.
8. BJÖRK, V. O., MALSTRÖM, G., AND UGGLA, L. G.: Left auricular pressure measurements in man. *Ann. Surg.* **138**: 718, 1953.
9. COBLENTZ, B., HARVEY, R. M., FERRER, M. I., COUNNAND, A., AND RICHARD, D. W.: The relationship between electrical and mechanical events in the cardiac cycle of man. *Brit. Heart J.* **11**: 1, 1949.
10. LIND, J., AND WEGELIUS, C.: The relationship between electrical and mechanical events in the heart as demonstrated by angiocardiology. *Univ. Michigan M. Bull.* **22**: 447, 1956.
11. ARVIDSSON, H., AND ÖDMAN, P.: Angiocardiology in mitral disease. *Acta radiol.* **47**: 97, 1957.
12. WILDER, R. J., MOSCAVITZ, H. L., AND RAVITCH, M. M.: Transventricular and aortic angiocardiology and physiologic studies in dogs with experimental mitral and aortic insufficiency. *Surgery* **40**: 86, 1956.
13. FOX, I. J., WAKAI, C. S., CONNOLLY, D. C., AND WOOD, E. H.: Left atrial and ventricular pressure pulses in mitral valvular disease. *Proc. Staff Meet., Mayo Clinic* **31**: 126, 1956.
14. WYNN, A., MATTHEWS, M. B., McMILLAN, I. K. R., AND DALEY, R.: The left auricular pressure pulse in normals and in mitral valve disease. *Lancet* **2**: 216, 1952.
15. OWEN, S. G., AND WOOD, P.: A new method of determining the degree of mitral obstruction: An analysis of the diastolic part of indirect left atrial pressure tracings. *Brit. Heart J.* **17**: 41, 1955.
16. OWEN, I., AND FENTON, W. J.: *Clinical Society Transactions* **34**: 183, 1901.
17. HOLZKNECHT, G.: *Archiv. und Atlas der normalen und pathologischen Anatomie*. Hamburg, Lucas, Graefe, and Sillern, 1901.
18. BRIGDEN, W., AND LEATHAM, A.: Mitral incompetence. *Brit. Heart J.* **15**: 55, 1953.
19. ELKIN, M., SOSMAN, M. C., HARKEN, D. E., AND DEXTER, L.: Systolic expansion of the left auricle in mitral regurgitation. *New England J. Med.* **246**: 958, 1952.
20. LUISADA, A. A., FLEISCHNER, F. G., AND RAPPAPORT, M. B.: Fluorocardiography (electrokymography): II. Observations on normal subjects. *Am. Heart J.* **35**: 348, 1948.
21. LIAN, C., FACQUET, J., AND MINOT, G.: La radio-electrokymographie interpretation des courbes physiologiques, application au problems des cardiopathies valvulaires mitrals. *Arch. mal coeur* **41**: 727, 1948.
22. ANDERSSON, T.: Electrocardiography with simultaneous electrocardiography. *Acta radiol.* **30**: 36, 1948.
23. MCKINNON, J. B., AND FRIEDMAN, B.: Electrocardiographic studies of the left atrium in normal and diseased hearts. *Circulation* **2**: 572, 1950.
24. DACK, S., AND PALEY, D. H.: Electrocardiography: II. The great vessel and auricular electrokymograms. *Am. J. Med.* **12**: 447, 1952.

25. LIAN, C., AND RAGER, C.: Un signe pathognomonique de l'insuffisance mitrale pure la courbe radio-electro-kymographique de reflux auriculaire gauche. *Semaine d. Hôp.*, Paris 30: 19, 1954.
26. SALDANHA, A., BETTENCOURT, J. M., PINTO, P. M., SCHRECK, M., AND FRAGOSO, J. C. B.: L'electrokymogramme de l'oreillette gauche a l'etat normal et pathologique, en particulier chez les mitraux, *Cardiologie* 25: 212, 1954.
27. HARING, O. M., TRACE, H. D., AND LUISADA, A. A.: Diagnosis of Mitral Stenosis by Electrokymography of the Left Atrium. Henry Ford Hospital, International Symposium on Cardio-Vascular Surgery. Philadelphia, W. B. Saunders Co., 1955, p. 156.
28. FLEISCHNER, F. G., ABELMAN, W. H., AND BUKA, R.: Value of the atrial electrokymogram in the diagnosis of mitral regurgitation. *Circulation* 10: 71, 1954.
29. DUSSAILANT, G., LEPE, A., AND GOMEZ, G.: Electro-kymogramme ventriculaire et auriculaire gauche, chronologie ventriculaire et arterielle chez les sujets normaux. *Acta cardiol.* 7: 38, 1952.
30. TAHAN, R. J., AND OOSTHUIZEN, S. F.: Electrokymography: A study of heart border motion in health and disease. *South African J.* 27: 1005, 1953.
31. DUSSAILANT, G., LESSANDI, H., AND LEPE, A.: Applications cliniques de la methode electrokymographique. *Acta cardiol.* 7: 473, 1952.
32. DAVISON, P. H., AND EPPS, R. G.: The left auricular electrokymogram in mitral stenosis. *Brit. Heart J.* 16: 49, 1954.
33. HARING, O. M., LIU, C. K., AND TRACE, H. D.: The left atrial pressure pulses in experimental mitral valve lesions. *Circulation* 4: 381, 1956.
34. LASSER, R. P., EPSTEIN, B., AND LOEWE, L.: Esophageal pressure pulse patterns (esophageal piezocardiogram): II. Observations in human beings with mitral valve disease. *Am. Heart J.* 44: 681, 1952.
35. ZOOR, M.: The esophageal pulse in mitral valve disease. *Brit. Heart J.* 16: 59, 1954.
36. ÖDMAN, P.: Electrokymographic studies of normal and abnormal right auricles. *Acta radiol.* 44: 353, 1955.



Heinz, R., and Abrams, H. L.: Radiologic Aspects of Operable Heart Disease. IV. The Variable Appearance of Constrictive Pericarditis. *Radiology* 69: 54 (July), 1957.

The authors on the basis of 21 cases proved at surgery come to the conclusion that no characteristic roentgenologic picture exists, that the typical small heart was present about half of the time, while the others were moderately or even markedly enlarged. Right ventricular and atrial enlargement occurred in 11 of 16 cases. Pulmonary artery dilatation involving the trunk and hilar branches occurred frequently, as did pulmonary congestion. The superior vena cava was frequently observed to be dilated, often involving also the adjacent azygos vein. Pulsations were regarded as of diminished amplitude in two thirds of the cases. Kymographie tracings indicated an increased period of diastolic filling with a long, flat diastolic plateau, while the amplitude of excursions was significantly decreased in most cases. Four had distinctly normal pulsations, even though subsequent surgery indicated considerable pericardial thickening. The authors suggest that based on the presented evidence that such roentgenologic observations as cardiac enlargement, normal pulsations, and pulmonary arterial widening should not be considered incompatible with the diagnosis of constrictive pericarditis when clinical observations to the contrary are present.

SCHWEDEL

Ventricular Precontracting Area in the Wolff-Parkinson-White Syndrome

Demonstration in Man

By GIULIO BANDIERA, M.D., AND PIER FAUSTO ANTOGNETTI, M.D.

By means of the analytic method of roentgenkymography of Cignolini, 11 typical cases of Wolff-Parkinson-White syndrome were studied. Comparison of the kymographic tracings with the synchronously registered electrocardiogram demonstrated precocious contraction of a limited ventricular area, situated in the left ventricle in the A type and in the right ventricle in the B type.

IN THE Wolff-Parkinson-White syndrome (W-P-W) the recognized causes of the pathognomonic electrocardiographic slow wave (the so-called *delta* wave) inserted between P and R are premature excitation of a ventricular area and an exceptionally slow transmyocardial conduction of the impulse, before it reaches the Purkinje network, and hence the whole of the myocardium.¹ It has been experimentally verified that such conduction may occur in a peculiar way in a few limited ventricular areas localized in the arterial cone of the heart, and chiefly in the right or left ventricular area adjacent to the anterior segment of the interventricular septum, close to the base.²

According to some authors, activation may originate in the septum; however, it diffuses first to one ventricle and then to the other. Following the conception of Rosenbaum et al., it would diffuse firstly to the left ventricle in the so-called A type (positive QRS in V_1 , V_5 , V_6) and to the right one in the B type (negative QRS in V_1 , V_5 , V_6).³

Since investigative procedures employed to date (jugular phlebography, cardiac sphygmography, roentgenkymography, electrokymography, etc.) have yielded uncertain and inconstant data on the mechanical effects of the ventricular pre-excitation phenomenon, a study employing Cignolini's analytic method of roentgenkymography^{4,5} was undertaken. By this method it is possible to obtain detailed graphs that reflect the movement of almost

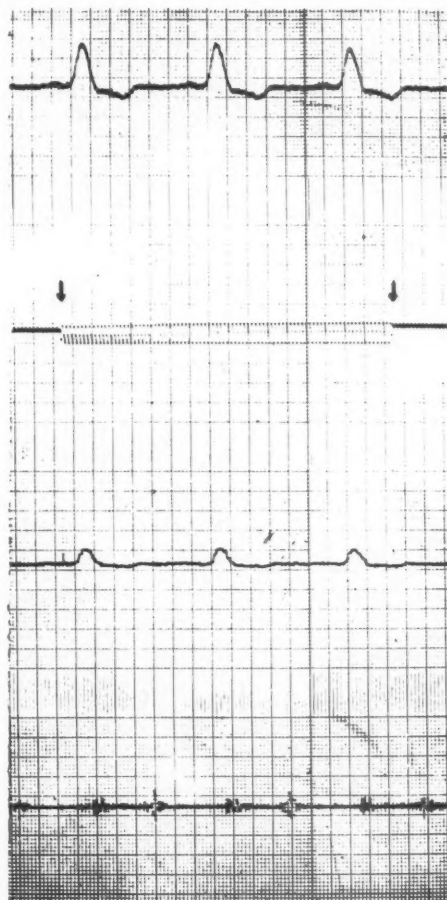


FIG. 1. Method of timing the duration of x-ray emission (second line) and synchronizing it with the electrocardiogram (first and third lines) and the phonocardiogram (fourth line). Time intervals, 0.02 second.

From Medical Clinic of the University, Genoa, Italy.

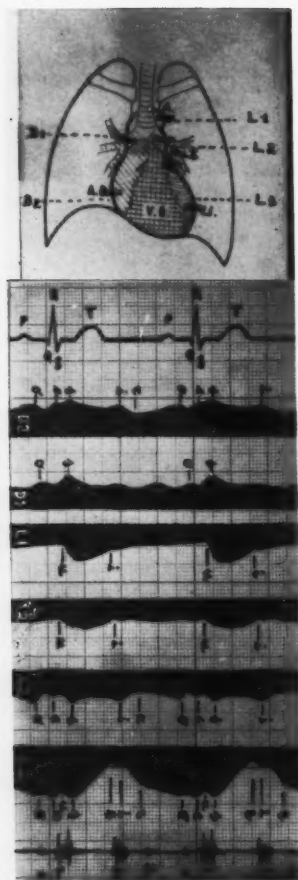


FIG. 2. Diagram of the normal roentgenkymographic tracings compared with the electrocardiogram and phonocardiogram. Time intervals 0.02 second.

every point of the cardiovascular profile and are always chronologically comparable among themselves together with synchronously registered electrocardiograms^{6, 7} (figs. 1 and 2). Moreover, the single ventricular areas can be observed directly and not indirectly by means of the movements of the great vessels caused by them. This last method, though extensively utilized by many workers, is obviously incorrect, inasmuch as any given ventricular area may contract prematurely without causing a pressure gradient high enough to open the semilunar valves. This has been proved experimentally by Prinzmetal et al.;⁸ they stim-

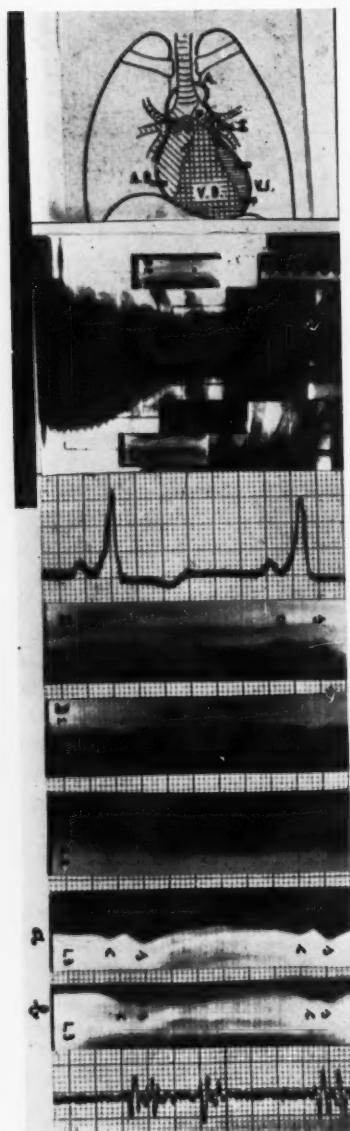


FIG. 3. Case of W-P-W syndrome, A type. Note the position of the *c* point (beginning of the ventricular contraction) in the higher section (*a*) and in the lower section (*b*) of the left ventricle; *o* = beginning of the atrial contraction; *s* = protosystolic wave. Time intervals 0.02 second.

ulated the epicardial or endocardial surface of both ventricles electrically and produced the W-P-W pattern; a filmed record of the

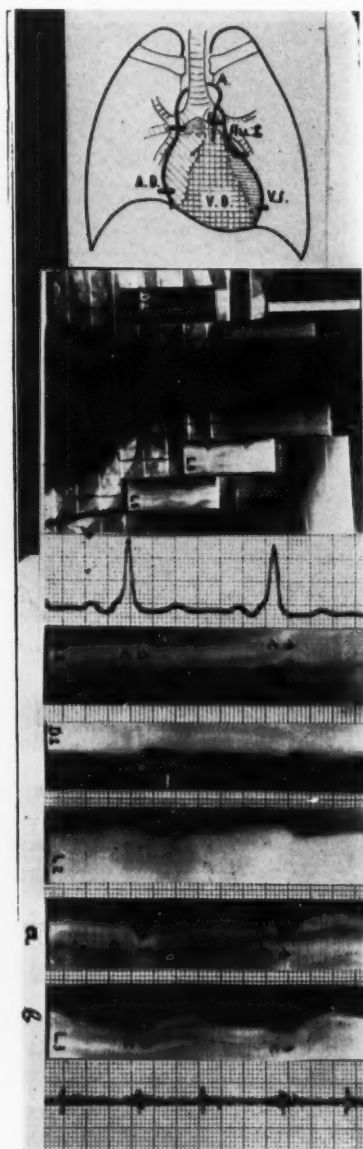


FIG. 4. Another case of W-P-W syndrome, A type.

contraction of the heart showed that in W-P-W systoles the mechanical activity of the heart was distinctive. Atrial contraction was normal, but it was not followed by the normal pause. On the contrary, ventricular activity followed immediately and 4 phases were rec-

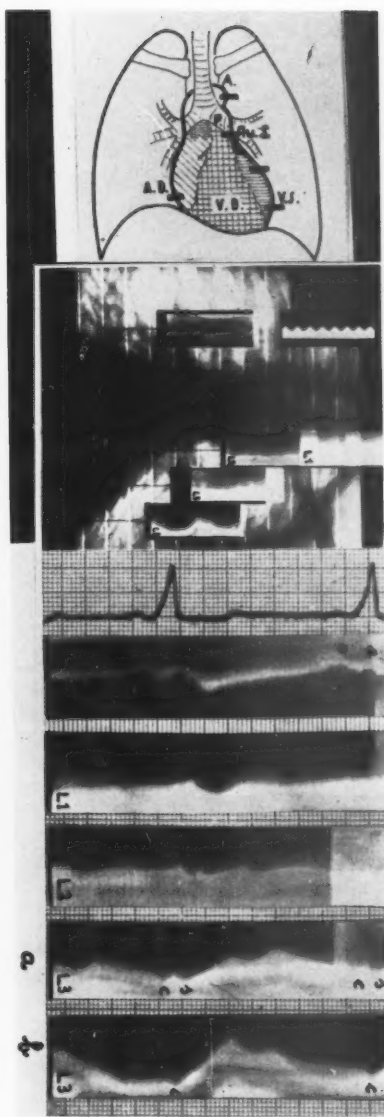


FIG. 5. Another case of W-P-W syndrome, A type.

ognized: (1) premature contraction of the electrically activated myocardial area followed by a discontinuous diffusion of the contraction wave to the surrounding areas (no blood ejection from the ventricle takes place in this phase); (2) contraction of the remain-

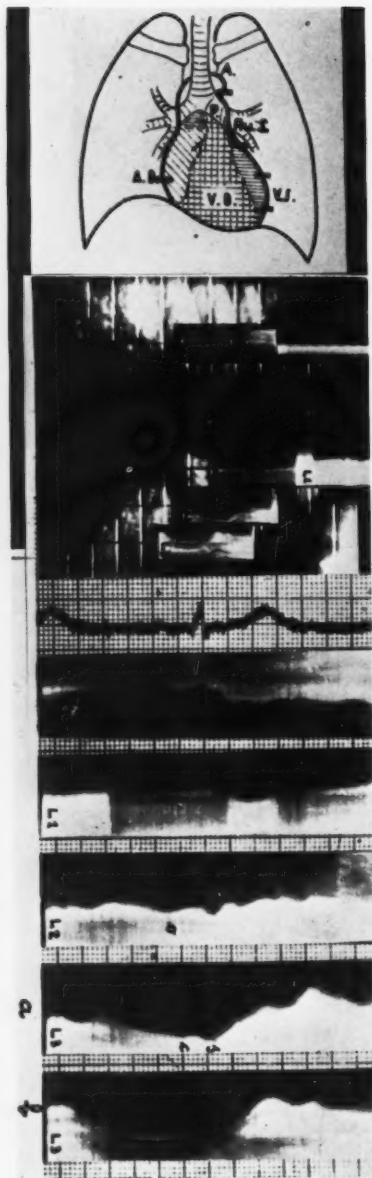


FIG. 6. The same case as that in figure 5, after the disappearance of the electrocardiographic abnormalities. The precontraction still persists.

ing ventricular myocardium, which occurred rapidly, as in normal systoles; (3) diastolic relaxation and protrusion of the precon-

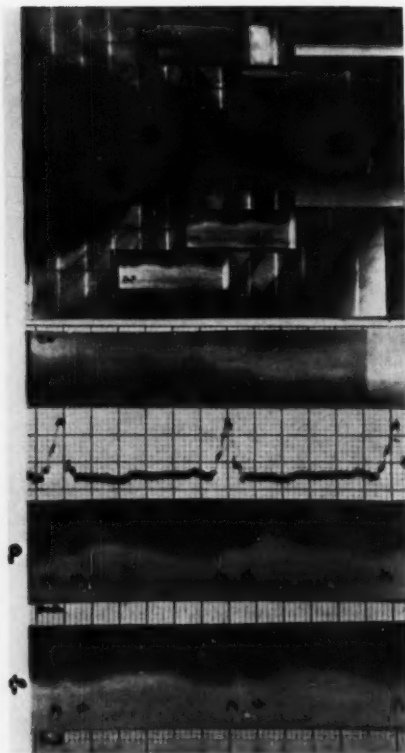


FIG. 7. Another case of W-P-W syndrome, A type.

tracted area, while the remaining ventricular muscle was still contracted; (4) occurrence of diastole.

ROENTGENKYMOGRAPHIC STUDIES

In a series of typical cases, detailed roentgenkymographic tracings were performed. Apart from variations in general morphology corresponding to the different physical types of the patients, a peculiar abnormality was detected, which we believe to be almost pathognomonic of the syndrome (figs. 3-10).

This consisted of a very clearly premature onset of the ventricular contraction (so-called point *c*) in the higher section of the left ventricle in the A type and of the right ventricle in the B type. The significance of this finding was indicated by the fact that this *c* point was earlier, by .04 to over .08 second, than the corresponding one in the lower sections of the same ventricle (fig. 11). In con-

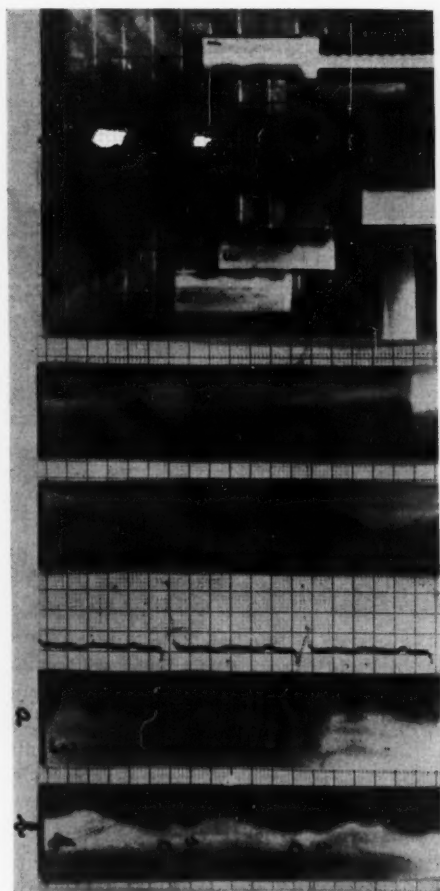


FIG. 8. The same case as that in figure 7, after the disappearance of the electrocardiographic abnormalities.

trast, the *c* point of the lower ventricular sections occurred about .03 second after the onset of QRS, as occurs in normal beats.

In other words, it is clear that the lower sections of the ventricles are not late in starting to contract. Contrariwise, the higher sections begin contracting much earlier, coincident with the abnormal *delta* wave on the electrocardiogram. In placing the *c* point, it should be kept in mind that the onset of systole, which is represented by the apex of the angle composed by the diastolic and systolic boundaries of the ventricular tracings, is closely followed by the protosystolic wave *s*.

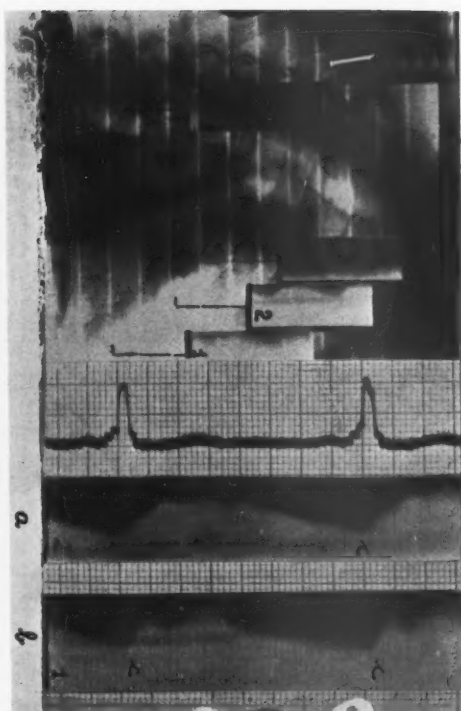


FIG. 9. Case of W-P-W syndrome, B type; records taken in the right anterior oblique position. Note a premature contraction in the higher section of the right ventricle.

This last, which is scarcely recognizable in the proximity of the cardiac apex, becomes more evident toward the base, where it often makes up the outer point of the whole tracing. It may also be noted that *s* wave, which is not the expression of a local contraction, but an effect of the whole ventricular systole, is rarely asynchronous in the different sections of the heart. Furthermore, the great vessels widen in a normal chronologic sequence after the ventricular contraction. The atrial waves also are normal in morphology and chronology. Every other roentgenkymographic component is quite normal.

In some cases a kymogram was recorded after the electrocardiographic abnormalities disappeared following intravenous procaine amide. In these tracings the precontraction was also clearly recorded (figs. 6, 8 and 10).

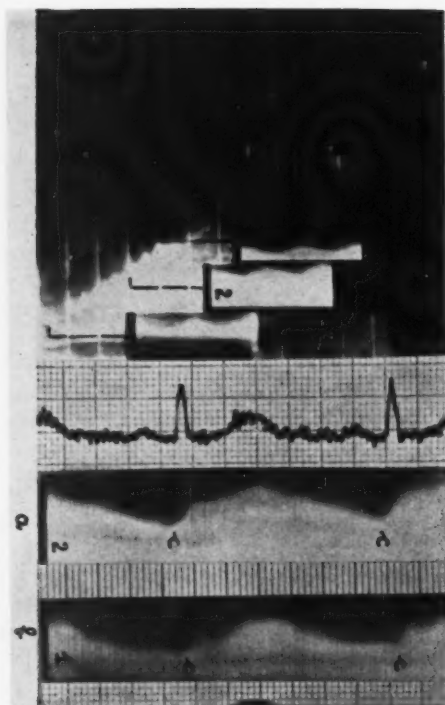


FIG. 10. The same case as that in figure 9, after the disappearance of the electrocardiographic abnormalities. The precontraction still persists.

However, it was not always possible to demonstrate the ventricular precontraction area in all cases: this was possible in 8 of our 11 cases. This failure occurred because the area was exceedingly small or was situated in points scarcely controllable by the kymographic analysis, especially in the B type of W-P-W syndrome. Moreover, as already stated, the degree of precontraction may change (in our cases from .04 to .08 second), sometimes even in the same subject.

DISCUSSION

It may be concluded that the kymographic tracings clearly confirm the existence of a "precontraction area," situated in the arterial cone of the left ventricle in the W-P-W syndrome A type, and of the right ventricle in the B type. It seems, accordingly, that the arrival of a premature excitation at a

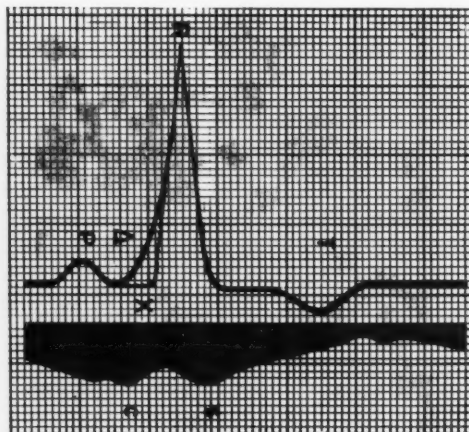


FIG. 11. Relationship between electrocardiogram and roentgenkymogram of the ventricular precontraction area. Time intervals 0.01 second.

limited area of the ventricular myocardium is definitely demonstrated also in man. The *delta* wave is the expression of the slow progression of the impulse from the pre-excited area to the adjacent ventricular myocardium. Despite the delay produced by this phenomenon, the excitation reaches the whole ventricular myocardium earlier than the impulse traveling along the Tawarian pathways (fig. 12). When the electrocardiogram does not show the typical abnormalities of the syndrome, it may be assumed that pre-excitation and precontraction still exist in a given ventricular area, but the excitation reaches the remaining ventricular myocardium by way of physiologic pathways and the impulse arising in the abnormal area is blocked.

In summary, it is evident that in W-P-W syndrome there exist 2 pathways of ventricular excitation. The anomalous pathway, of anatomic or simply functional nature, conducts the impulse faster than the normal one, so that the excitation reaches the ventricles earlier, and particularly an area located near the base of the right or left ventricle. While this area contracts the excitation passes to the remaining ventricular myocardium with a certain delay (*delta* wave), but always faster, however, than the normal impulse, traveling along the normal path-

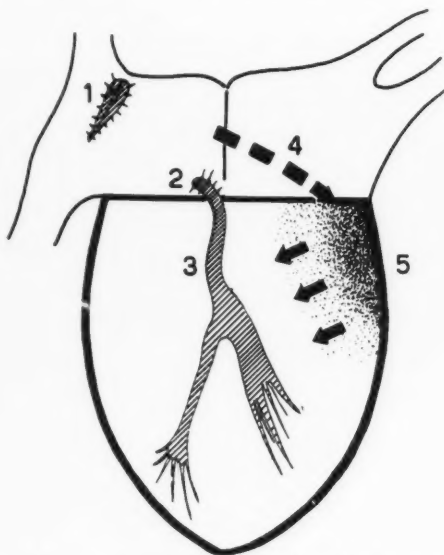


FIG. 12. Diagram of the 2 atrioventricular conduction pathways in the W-P-W syndrome (5: precontraction area).

ways, which, therefore, finds the ventricles already in a refractory state.

When, either spontaneously or by means of pharmacologic agents, the impulse arising from the pre-excited area is blocked, the ventricles are excited in the normal way: but the ventricular precontraction still persists.

SUMMARY

Studies carried out in the Wolff-Parkinson-White syndrome by means of the analytic roentgenkymography have shown for the first time in man a precocious contraction of a limited ventricular area, which is situated in proximity of the base, in the left ventricle in the A type and in the right ventricle in the B type.

SUMMARIO IN INTERLINGUA

Studios effectuata in patientes con syndrome de Wolff-Parkinson-White per medio de roentgenokymographia analytic ha producite le prime demonstration del occurrentia in humanos de un contraction precoce in un area restringite del ventriculo. Iste area es situate in le proximitate del base in le ventriculo sinistre in typo A e in le ventriculo dextere in typo B.

REFERENCES

1. SEGERS, M., LEQUIME, J., AND DENOLIN, H.: L'activation ventriculaire précoce de certains coeurs hyperexcitables. Etude de l'onde delta de l'électrocardiogramme. *Cardiologia* 8: 113, 1944.
2. FRAU, G., AND MAGGI, G. C.: La sindrome di Wolff-Parkinson-White. Reggio Emilia, A. Recordati, 1954.
3. ROSENBAUM, F. F., ILECHT, H. H., WILSON, F. N., AND JOHNSTON, F. D.: The potential variations of the thorax and the esophagus in anomalous atrio-ventricular excitation (Wolff-Parkinson-White syndrome). *Am. Heart J.* 29: 281, 1945.
4. CIGNOLINI, P.: Roentgenchimografia cardiaca e regmografia. Bologna, Cappelli, 1934.
5. —: Roentgenchimografia analitica cardiaca. *Radiologia Practica*, 4, 1952.
6. ANTognETTI, P. F., AND BANDIERA, G.: Roentgenchimografia analitica cardiaca. Studio morfocronologico delle grafiche rilevabili nelle varie proiezioni con registrazione contemporanea di elettro e fonocardiogramma. *Arch. Maragliano* 8: 1219, 1953.
7. BANDIERA, G., AND ANTognETTI, P. F.: Rilievi di roentgenchimografia analitica nelle turbe del ritmo e della conduzione. *Folia cardiologica* 13: 293, 1954.
8. PRINZMETAL, H., KENNAMER, R., CORDAY, E., OSBORNE, J. A., FIELDS, J., AND SMITH, L. A.: Accelerated conduction. The Wolff-Parkinson-White syndrome and related conditions. New York, Grune and Stratton, Inc., 1952.



Patent Ductus Arteriosus in Association with Pulmonic Stenosis

A Report of Six Cases with Additional Noncardiac Congenital Anomalies

By DOUGLAS C. HEINER, M.D., AND ALEXANDER S. NADAS, M.D.

A review was made of patients recently seen at the Children's Medical Center, Boston, who qualified for the diagnosis of patent ductus arteriosus associated with pulmonic stenosis. Six such patients were observed. The cardiac findings were distinctive, allowing for presumptive diagnosis without catheterization in the majority of instances. Noncardiac congenital anomalies of a particular type were found to be a part of the clinical profile. This finding plus certain epidemiologic evidence suggests the possibility of a common etiologic factor.

PATENT ductus arteriosus and pulmonic stenosis as individual lesions are among the commonest of congenital defects of the heart, each constituting 10 to 15 per cent of congenital cardiac anomalies.¹ A combination of the 2 has been thought to be relatively uncommon. Eckstrom² found that of 255 patients carefully evaluated following operative repair of a patent ductus arteriosus, 17, or 6 per cent of the total, were found to have a murmur with a cause demonstrable by right heart catheterization. Twelve (4.7 per cent) had a significant gradient between the right ventricle and the pulmonary artery, indicating the presence of pulmonic stenosis. Gross³ performed simultaneous pulmonary valvotomy on 3 of 525 patients operated upon for a patent ductus arteriosus. He likewise observed that about 6 per cent of his patients had a persistent organic murmur following surgery for patent ductus arteriosus.

The purpose of this paper is to report our findings in patients with patent ductus arteriosus and pulmonic stenosis, to point out how these findings differ from those in patients with either lesion alone, and to discuss the possible significance of certain associated noncardiac anomalies that have been observed.

MATERIAL AND METHODS

A review of recent experience (1945-1956) in this hospital revealed 6 patients with good evidence of a

patent ductus arteriosus and associated pulmonic stenosis. All 6 have been operated upon for repair of the patent ductus and have had findings during operation and in the postoperative period indicating the presence of pulmonic stenosis. Four of these children were also subjected to cardiac catheterization preoperatively.

Careful histories, physical examinations, routine laboratory studies, chest x-rays, fluoroscopy, and electrocardiograms were done on all patients. The methods and instruments used at cardiac catheterization were described in previous reports from this department.^{4, 5}

CASE HISTORIES

Case 1. R. V. This boy was born following an apparently normal full-term pregnancy with no known evidence of maternal trauma, rubella, or other infections. He was thought to be normal at birth but has always been underweight for his age. Speech and hearing difficulties were present from early life, and he has consistently been slow in school work.

A murmur was discovered at the age of 3 years when he was taken to a physician because of "fainting spells." The fainting spells have not recurred.

On hospitalization at the age of 9, physical examination revealed his height and weight each to be under the third percentile on our developmental charts.⁶ Head circumference was 18.3 inches. The second heart sound was diminished in the pulmonic area and was narrowly split. A grade IV continuous murmur was heard in the second left and right interspaces and a separate, rough stenotic grade V systolic murmur was heard along the left sternal border, transmitting well to the neck and upper back. Additional findings are outlined in tables 1-3 and a preoperative electrocardiogram is shown in figure 1.

A diagnosis of patent ductus arteriosus with pulmonic stenosis was made. At operation, the

From the Department of Pediatrics, Harvard Medical School and the Sharon Cardiovascular Unit, Children's Medical Center, Boston, Mass.

TABLE 1.—Catheterization Data

Patient number	Pressures (mm. Hg)						Oxygen content (vol. %)						Cardiac index (L./min./M. ²)			Resistance (dynes-sec.-cm. ⁻²)	
	Pulmonary artery (syst./diast.)	Pulmonary artery (mean)	Right ventricle (syst./diast.)	Right atrium (mean)	Brachial artery (syst./diast.)	Brachial artery (mean)	Pulmonary artery	Right ventricle	Right atrium	Superior vena cava	Brachial artery	Oxygen capacity	Pulmonary index	Systemic index	Net shunt index (left-to-right)	Pulmonary vascular	Systemic
6.	37/20	27	58/0	3	100/47	75	13.9	11.3	11.5	12.1	14.9	15.3	18.2	5.0	13.2	180	2600
2.	21/13	17	72/6	0	125/55	88	11.4	9.9	9.8	10.1	14.1	14.2	6.3	4.0	2.3	270	3200
1.	16/9	13	97/0	4	105/60	69	13.9	12.4	13.4	12.4	15.8	15.8	7.7	3.7	4.0	73	1400
4.	90/55	65	100/12	11	122/55	75	14.0	9.4	8.1	8.9	15.7	16.0	19.0	3.5	15.5	260	2130
(pre-op)																	
4.	26/7	17	42/3	9	115/64	80	13.1	NSR*	13.2	12.9	NSR	NSR	5.1	5.1	0	136	1210
(post-op)†																	

* NSR = No sample recorded.

† Patent ductus arteriosus divided.

TABLE 2.—Factors Possibly Related to Etiology

Patient number	1	2	3	4	5	6
History of maternal rubella in early pregnancy.....			X		X	?
Birth date.....	Dec. '46	Dec. '51	Oct. '42	Mar. '43	Jan. '44	Jan. '54
Birth place.....	Vt.	Mass.	Me.	Mass.	Mass.	Me.
Mental retardation.....	X		X	X	X	
Motor retardation.....		X		X	X	X
Microcephaly.....	X			X		
Eye abnormalities.....			X	X		X
Hearing deficit.....	X	X				
Birth weight.....	5 ^a	5 ²	5 ⁰	6 ³	5 ⁸	5 ¹⁴
Height preop. (percentile).....	<3	5	<3	<3	<3	<3
Weight preop. (percentile).....	<3	25	<3	<3	<3	<3

patent ductus arteriosus was divided and a pulmonary valvotomy was performed. Evaluation in the immediate postoperative period revealed absence of the continuous murmur, a persistence of the rough stenotic murmur, and no significant change in the electrocardiogram.

Case 2. R. C. Maternal pregnancy and delivery were thought to be normal. The patient was seen at Children's Medical Center at 19 months of age for evaluation of hearing difficulty. Audiometric tests revealed an 85 to 100 decibel loss bilaterally. Since then he has been followed in the congenital heart clinic where he has been noted to have frequent respiratory infections but to be active and without other cardiac symptoms.

At 2 $\frac{1}{2}$ years of age his arm blood pressure was 125/55. His pulmonic second sound was well split and of normal intensity. There was a grade V rough

stenotic systolic murmur heard best in the supra-sternal notch and a grade IV continuous murmur in the second left interspace. Further findings are outlined in tables 1-3. A preoperative electrocardiogram is shown in figure 1.

The diagnosis of patent ductus arteriosus with pulmonic stenosis was made. At surgery, a patent ductus arteriosus was divided and pulmonary valvotomy was performed. Preoperative and postoperative chest roentgenograms are shown in figures 2 and 3.

At age 3 $\frac{1}{2}$ the patient was asymptomatic except for hearing and speech difficulties. Blood pressure was 110/70. A thrill was palpable in the second left interspace and a grade III to IV rough systolic murmur was heard in this area, transmitting to the neck and upper back. Chest x-ray revealed a reduction in the previous cardiac enlargement and

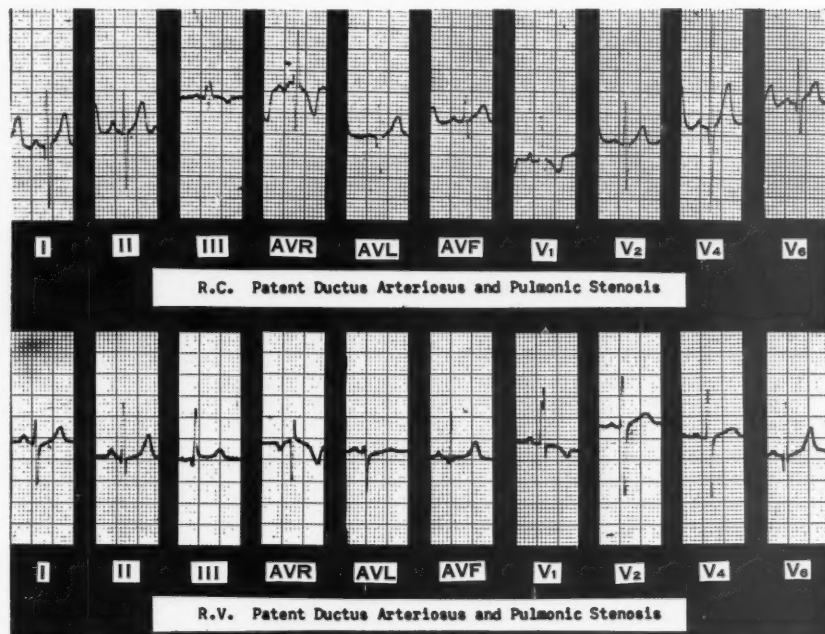


FIG. 1. Preoperative electrocardiograms showing right axis deviation and right ventricular hypertrophy in patients who had 81 and 51 mm. Hg peak systolic pressure gradients, respectively, across the pulmonic valve.

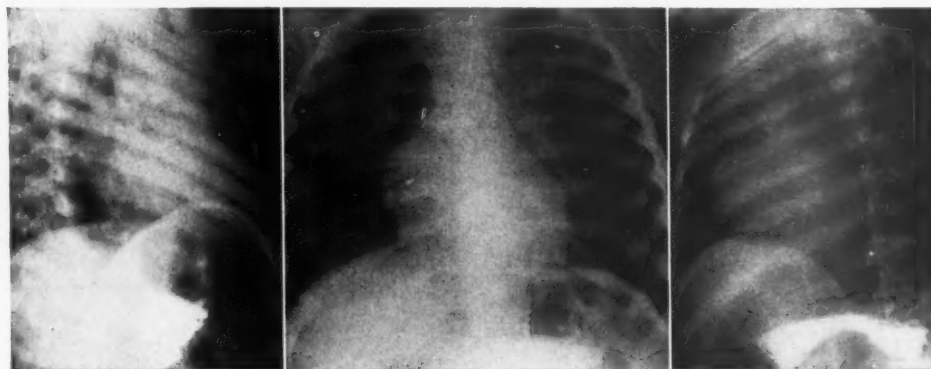


FIG. 2. Preoperative roentgenograms of patient no. 2 with patent ductus arteriosus and pulmonic stenosis. There is slight cardiomegaly but pulmonary vascularity appears within normal limits. *Left*, right anterior oblique; *middle*, posteroanterior; *right*, left anterior oblique.

figure 5, revealing a progression from left ventricular hypertrophy preoperatively to right ventricular hypertrophy postoperatively.

Case 4. F. K. The first trimester of gestation was complicated by frequent episodes of vomiting but there was no history of German measles or other infections. Delivery was at term, resulting in an

infant with bilateral congenital cataracts. Weight gain was always slow even though her appetite was adequate. She first sat at 18 months, began walking at 3 years. She has had frequent respiratory infections, easy fatigability, and dyspnea on moderate exertion.

Physical examination at 7 years of age revealed a



FIG. 3. Roentgenogram of patient no. 2, 1 year postoperatively.

wandering nystagmus and bilateral aphakia, the result of operative removal of cataracts. A grade IV rough systolic murmur was heard along the left sternal border and transmitted well to the neck and upper back. A grade III middiastolic rumble was heard at the apex. Some observers, in addition, heard a continuous murmur in the pulmonic area. Additional findings are noted in tables 1-3.

At age $7\frac{1}{2}$ the ductus arteriosus was divided. Studies several years later showed her to be in the twentieth percentile for weight and the twenty-fifth percentile for height (preoperatively she was below the third percentile for both height and weight). There was a grade II rough systolic murmur in the pulmonic area. The second sound was rather widely split but of normal intensity. Electrocardiograms have shown a disappearance of left ventricular hypertrophy but a persistence of incomplete right bundle-branch block. Postoperative catheterization data are included in table 1.

Case 5. L. R. This girl's mother was known to have had German measles approximately 1 month after conception. Pregnancy was otherwise uneventful as was delivery at full term. Developmental retardation was evidenced by poor weight gain and slow linear growth, inability to sit unassisted until after 18 months of age, markedly delayed onset of walking, and marked slowness in school.

Preoperative physical examination revealed a grade III to IV murmur with systolic crescendo and diastolic decrescendo heard best in the pulmonic area, having a rough systolic element transmitting well to the upper back. Separate systolic and diastolic murmurs were heard at the apex (tables 1-3). Only standard limit leads were taken in preoperative electrocardiograms.

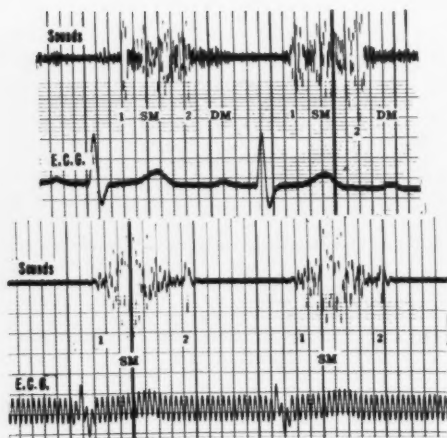


FIG. 4. Phonocardiograms in patent ductus arteriosus and pulmonic stenosis showing a continuous murmur preoperatively (*top*) in the second left interspace. In the lower tracing a diamond-shaped systolic murmur is seen to persist after division of a patent ductus arteriosus and pulmonic valvotomy.

At 19 months of age the patent ductus arteriosus was divided and at operation it was noted that a systolic thrill persisted over the pulmonary artery. A valvotomy was not performed. Cardiac catheterization has not been obtained. Numerous postoperative examinations over a 10-year period have shown the existence of a rough systolic murmur in the pulmonic area well transmitted to the neck and back. Electrocardiogram 5 years postoperatively showed an axis of $+115^\circ$ with definite right ventricular hypertrophy.

Case 6. V. T. This girl's mother had a febrile illness without rash when 2 months pregnant, at a time when a son in the family and others in the community had typical German measles. The prenatal course and delivery were otherwise normal. Congenital cataracts were noted at birth and were surgically removed at 18 months. The patient did not walk until 2 years of age. There have been frequent respiratory infections all her life including pneumonia 3 times during her second year. Exercise tolerance has been normal.

Physical examination showed her to be underdeveloped and undernourished. There was bilateral aphakia and lateral nystagmus. A grade IV rough systolic murmur was heard maximally in the pulmonic area and suprasternal notch and was well transmitted to the neck and upper back. A grade III continuous high frequency murmur was present under the left clavicle and a grade III middiastolic rumble was heard at the apex (tables 1-3).

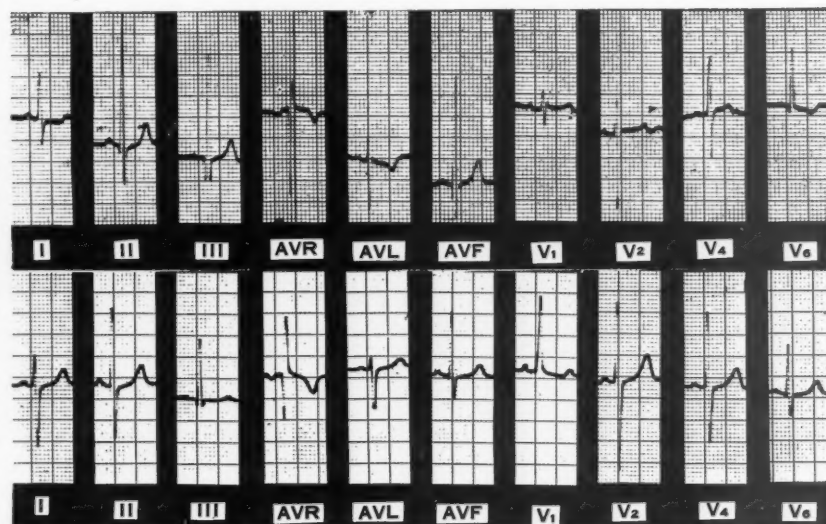


FIG. 5. Preoperative (*top*) and postoperative (*bottom*) electrocardiograms in patient no. 3 showing disappearance of left ventricular hypertrophy and the emergence of right ventricular hypertrophy after division of the patent ductus arteriosus. Valvotomy was not performed.

CLINICAL FEATURES

A history of rubella in early pregnancy was present in 2 of the 6 mothers and possibly in a third. Each patient was born in New England, the birth dates lying between October 29 and March 21. Four of the 6 patients weighed $5\frac{1}{2}$ lb. or less at birth, and the largest was $6\frac{3}{16}$ lb., although none was considered premature by expected date of confinement calculations. All continued to be below average in growth, 5 being under the third percentile for both height and weight at the time of operation. A growth spurt was noted in 2 postoperatively (patients 3 and 4). A heart murmur was heard within the first 3 months of life in 4 patients. Two had some dyspnea on exertion preoperatively, but 4 had no limitation of activity at any time. Four had frequent respiratory infections and 2 had a history of syncope in early life. None had a history of cyanosis or congestive failure. Associated congenital anomalies were present in each patient and are included in table 2.

Pulse pressures were in excess of 40 mm. Hg in all patients. The cardiac impulse, recorded preoperatively in 5 patients, was described to be maximal near the xiphoid in 1 patient and prominent at both the xiphoid and the apex in

the other 4. The first heart sound was not recorded as being abnormal in any patient. The second sound had variable characteristics, in some instances being diminished in intensity in the pulmonic area without audible splitting. A continuous machinery-like murmur was heard in all patients but in some instances was rather difficult to make out because of the superimposed murmur of pulmonic stenosis. This latter rough, stenotic murmur was recognized in the second left interspace and had good transmission to the suprasternal notch, neck, and upper back in 5 patients preoperatively, and in all patients postoperatively. A suprasternal thrill was palpable more frequently than in our experience in patients with isolated patent ductus arteriosus. A diastolic murmur was not heard postoperatively in any patient. Typical preoperative and postoperative phonocardiograms are presented in figure 4.

Preoperative electrocardiograms included chest leads in 5 of the patients and revealed evidence of isolated right ventricular hypertrophy in 2 (fig. 1), combined right and left hypertrophy in 2, and left ventricular hypertrophy associated with incomplete right bundle-branch block in a fifth patient (fig. 5).

Postoperative electrocardiograms in 5 patients showed right axis deviation and isolated right ventricular hypertrophy in 4; the fifth patient showed incomplete right bundle-branch block with disappearance of the left ventricular hypertrophy, which was present in the pre-operative tracing (fig. 5).

Cardiac Catheterization

Catheterization revealed definite evidence of pulmonic stenosis on withdrawal from the pulmonary artery in each of the 4 patients so examined (table 1). Peak systolic pressure gradients between the right ventricle and the pulmonary artery varied from 10 to 81 mm. Hg. A jump of more than 1.0 volume per cent in O₂ content at the pulmonary artery level compared with the right ventricle was found in each instance.

Operative Findings

The patent ductus was divided in all 6 patients and a residual thrill was felt over the root of the pulmonary artery in each of 4 instances in which palpation of this area was recorded. Valvotomy was performed in 2 instances. No evidence of cardiovascular anomalies other than patent ductus arteriosus and pulmonic stenosis was found in any instance.

DISCUSSION

Etiology. There is evidence⁷⁻⁹ that a number of maternal diseases or stresses during pregnancy may lead to congenital defects in the offspring. One of these, rubella or German measles, requires special discussion in view of the clinical features found in our patients.

Gregg¹⁰ first called attention to the importance of rubella during pregnancy when he reported in 1942 congenital cataracts in 78 children born to mothers who had rubella during early gestation. Forty-four of these children also were said to have had congenital heart disease. The cardiac lesion proved to be a patent ductus arteriosus in most instances where a definite diagnosis was made. Murphy¹¹ in 1947 collected 295 instances of rubella in pregnancy being followed by a defective offspring. Cataracts were found in 161 patients,

congenital heart disease in 117, and deaf-mutism in 88. Campbell¹² in 1949 reported 250 patients with cyanotic congenital heart disease, stating that 3 resulted from pregnancies known to be complicated by maternal rubella; all 3 had pulmonic stenosis and a ventricular septal defect. One of the 3 had congenital cataracts. Rutstein et al.¹³ reported 27 patients with congenital heart disease whose mothers had rubella during pregnancy. A definite cardiac diagnosis was made in 18 of these patients, all of whom had a patent ductus arteriosus. (Subsequently it has been shown that at least 2 of these children had the combination of patent ductus arteriosus and pulmonic stenosis.) These authors emphasized the important point that in Massachusetts most rubella infections occur during the spring months and the majority of resultant defective children are born between October and March. This distribution of birthdays contrasts with that of patients with patent ductus arteriosus without a history of maternal rubella during pregnancy.¹³

Studies by a few authors¹⁴⁻¹⁷ have reported percentages of children who may be expected to be defective if born of mothers having known rubella in pregnancy. Ingalls¹⁸ has recently summarized these and other data and concluded that nearly 15 per cent of such infants will have congenital anomalies. Among these, patent ductus arteriosus is the most common cardiac lesion to be recognized.

Anderson¹⁹ found that noncardiac defects occurred in about half of his patients with patent ductus arteriosus and additional cardiac anomalies. Conversely, noncardiac congenital defects were found in only 14 per cent of patients with isolated patent ductus arteriosus. MacMahon and his co-workers²⁰ reported noncardiac defects in 10 per cent of all patients with patent ductus arteriosus.

Pulmonary stenosis is commonly associated with other cardiac anomalies, particularly ventricular septal defects. No references could be found in the literature citing the occurrence of noncardiac defects in patients with pulmonic stenosis. It is our impression, however, that noncardiac defects of the type reported in the present publication are quite rare in patients

with pulmonic stenosis, with or without associated cardiac lesions other than patent ductus arteriosus.

Thus, the fact that all 6 of the patients in whom we have proved the diagnosis of patent ductus arteriosus and pulmonic stenosis have had additional noncardiac defects of a particular type is interesting and suggests the possibility of a common etiologic factor in these patients. It should be emphasized that there is direct proof in only 2 instances (patients 3 and 5), and suggestive evidence in a third (patient 6), that the mothers of these patients had rubella during pregnancy. It is possible that other viral agents or noninfectious insults may have been etiologic factors in the remaining cases. Circumstantial evidence, however, may be in favor of rubella, particularly the fact that each patient's birthdate falls between October and March. Further support for such a hypothesis may come from the observation that a certain number of patients with congenital cataracts do not have a history of maternal rubella during pregnancy yet have birthdates clustered in the same period of time as similarly afflicted patients whose mothers did have rubella during pregnancy in an epidemic season.²¹ Krugman et al.²² and Anderson²³ have made observations dealing with the probability of rubella infections without a rash.

It is of interest that embryologically the ductus arteriosus and the pulmonary artery are each derived from the artery of the sixth branchial arch. Thus, it is not difficult to imagine that an insult during the differentiation of these structures might result in both an abnormal persistence of the patent ductus arteriosus and an abnormal evolution of the root of the pulmonary artery.

Clinical Cardiac Findings. The combination of patent ductus arteriosus and pulmonic stenosis results in cardiac findings that should allow accurate preoperative diagnosis in the majority of instances. Some features of each anomaly are present, the most prominent findings depending on the relative severity of each lesion. The machinery murmur is attributable to the patent ductus arteriosus as is an accentuated pulmonic component of the second heart

sound, pulmonary vasculature engorgement, evidence of left ventricular or left atrial hypertrophy, and frequent respiratory infections. Similarly, the presence of a rough stenotic systolic murmur and thrill in the second left interspace and suprasternal notch with maximal intensity during early or midsystole reflects the presence of pulmonic stenosis, especially if combined with a pulmonary closure of diminished intensity, a xiphoid cardiac impulse, and radiologic or electrocardiographic evidence of right ventricular hypertrophy.

A few patients have been observed in our clinic who presented a history of maternal rubella during pregnancy, whose birthdates have fallen between October and March, and who have had noncardiac anomalies similar to those described herein yet have been shown to have patent ductus arteriosus in association with pulmonary vascular obstruction without pulmonic stenosis. One similar patient had a patent ductus arteriosus with a stenotic murmur in the second right interspace and no gradient across the pulmonic valve at catheterization. She was presumed to have aortic stenosis; operation was not performed. In some instances these patients may be clinical diagnostic problems requiring catheterization to enable differentiation from patent ductus arteriosus and pulmonic stenosis. Careful physical examinations, however, reveal that pulmonary hypertension may usually be recognized by a markedly accentuated pulmonic second sound. The continuous murmur is absent if pulmonary vascular obstruction is severe. The presence of a stenotic murmur heard best to the right of the sternum and under the right clavicle leads to a suspicion of aortic stenosis.

Pathologic Physiology. For practical purposes the 2 anomalies discussed may be considered independent burdens on the 2 sides of the heart. The presence of a patent ductus arteriosus increases the volume work of the left ventricle and the left atrium without causing significant changes in intracardiac pressures. Pulmonary stenosis, on the other hand, increases systolic ejection pressure of the right ventricle without affecting the volume of blood passing through

unless there is severe stenosis and right ventricular failure.

Certainly the 2 lesions will not compensate for each other. In pulmonic stenosis without a right-to-left shunt, a patent ductus would merely recirculate fully oxygenated blood through the lungs and cause increased left ventricular work without alleviating right ventricular obstruction, improving cardiac output, or promoting peripheral oxygen transport. Therefore, in the patients described, there existed the usual indications for division of the patent ductus arteriosus plus the additional possibility of somewhat decreasing the work of the hypertensive right ventricle by decreasing pulmonary artery pressure.

Treatment. The need for surgical correction of each defect should be considered on the basis of the severity of the lesion and the operative risk.

Division of the patent ductus arteriosus—a safe surgical procedure—is recommended in all instances where a sizable left-to-right shunt is present.

If the existence of a significant degree of pulmonary stenosis is suggested by the clinical and electrocardiographic findings, cardiac catheterization should be performed preoperatively to determine more exactly the degree of obstruction caused by the stenotic lesion. If the gradient across the valve is great in relation to flow, or if right ventricular pressure exceeds 100 mm. Hg at rest, the patient should be considered a candidate for repair of both the patent ductus and the pulmonic stenosis. Frequently the risk of a combined operation on the 2 lesions may be less than that of 2 separate surgical interventions. Allowance should be made, however, for the possibility of lowering pulmonary arterial and even right ventricular pressures merely by ligating the ductus. It should be pointed out, also, that catheterization data do not provide the only basis for deciding upon valvotomy. Other factors are heart size (especially cardiomegaly not attributable to flow through the patent ductus), severity of right ventricular hypertrophy as indicated by the electrocardiogram, clinical evidences of right ventricular failure, and the presence of symptoms.

SUMMARY

Six patients with the combination of patent ductus arteriosus and pulmonic stenosis are presented. All of these children have been found, in addition, to have several noncardiac anomalies, including mental retardation, microcephaly, congenital cataracts, nystagmus, retinal degeneration, strabismus, and deaf-mutism. The identity of these anomalies with those seen in offspring after pregnancies complicated by rubella is suggestive of a common etiologic factor. The gestation of at least 2 of these patients was complicated by known rubella.

The coexistence of patent ductus arteriosus and pulmonic stenosis is usually recognizable clinically without angiocardiograms or cardiac catheterization. This combination of defects should be considered in patients with the diagnosis of either patent ductus arteriosus or pulmonic stenosis resulting from a pregnancy complicated by rubella, or in the presence of noncardiac defects of the type described. The clinical profile also includes delivery at full term with less than usual birth weight, a murmur audible in early infancy, and slow weight gain and linear growth. Cardiac examination usually reveals a wide pulse pressure, a continuous murmur in the second left interspace, and a separate rough systolic murmur and thrill maximal in the pulmonic area and supra-sternal notch, with good transmission to the neck and back. Electrocardiograms show right ventricular hypertrophy or incomplete right bundle-branch block, sometimes in combination with left ventricular hypertrophy. Radiologic examination shows moderate cardiomegaly involving both ventricles and usually the left atrium, with engorged pulmonary vasculature.

Division of the patent ductus is recommended in each instance. Patients with evidence of a significantly increased right ventricular work load should have preoperative cardiac catheterization to determine the need for simultaneous valvotomy.

ACKNOWLEDGMENT

We are indebted to Dr. Abraham Rudolph for a large part of the data obtained by cardiac catheteri-

zation, to Dr. Robert E. Gross and Dr. Luther Longino for allowing the use of their operative material, and to Dr. David Rutstein for providing his records of patients with patent ductus arteriosus having a history of maternal rubella during gestation.

SUMMARY IN INTERLINGUA

Es presentate 6 patientes pediatric con le combination de patente ducto arteriose e stenosis pulmonic. In omnes esseva trovate in plus un o plure anormalitates noncardiac, incluse retardation mental, microcephalia, cataractas congenite, nystagmo, degeneration retinal, strabismo, e surdemutismo. Le identitate de iste anormalitates con le anormalitates vidite in prole post pregnantias complicate per rubella suggere le presentia del mesme factor etiologic in le duo situationes. Le gestation de al minus 2 del presente patientes esseva complicate cognoscitemente per un episodio de rubella.

Le coexistentia de patente ducto arteriose e stenosis pulmonic es usualmente recognoscibile per medios clinic sin recurso a angiocardio-grammas o catheterisation cardiac. Iste combination de defectos debe esser suspicite in patientes con le diagnose de o patente ducto arteriose o stenosis pulmonic como resultado de pregnantia complicate per rubella o in le presentia de defectos noncardiac del typo describite. Le profilo clinic include etiam parturition a termino con peso natal infra le norma, un murmure audibile in le prime infantia, e lente augmentos de peso e de statura linear. Le examine cardiac revela usualmente un large pression de pulso, un murmure continue in le secunde interspatio sinistre, e un separate e aspere murmure e fremito systolic que attinge su maximo in le area pulmonic e del incisura suprasternal con bon transmission verso le nucha e le dorso. Electrocardiogrammas revela hypertrophia dextero-ventricular o incomplete bloco de branca dextere, a vices in combination con hypertrophia sinistro-ventricular. Le examine radiologic monstra moderate grados de cardiomegalia in ambe ventriculos e usualmente le atrio sinistre, con constipation del vasculatura pulmonar.

Le division del patente ducto arteriose es recommendate in omne tal casos. Patientes con

manifestationes de un augmento significative del labor dextero-ventricular debe esser subjecite a catheterisation cardiac pro determinar le necessitate del simultanee execution de valvotomia.

REFERENCES

- ¹ WOOD, P., MAGIDSON, O., AND WILSON, P. A. O.: Ventricular septal defect with a note on acyanotic Fallot's tetralogy. *Brit. Heart J.* **16**: 387, 1954.
- ² ECKSTROM, G.: The surgical treatment of patent ductus arteriosus. A clinical study of 290 patients. *Acta chir. scandinav. Suppl.* **169**: 1952.
- ³ GROSS, R. E.: The patent ductus arteriosus: observations on diagnosis and therapy in 525 surgically treated cases. *Am. J. Med.* **12**: 472, 1952.
- ⁴ BRAUDO, J. L., NADAS, A. S., RUDOLPH, A. M., AND NEUHAUSER, E. B. D.: Atrial septal defects in children: a clinical study with special emphasis on indications for operative repair. *Pediatrics* **14**: 618, 1954.
- ⁵ SILVERMAN, B. K., NADAS, A. S., WITTENBERG, M. H., GOODALE, W. T., AND GROSS, R. E.: Pulmonary stenosis with intact ventricular septum: Correlation of clinical and physiologic data, with review of operative results. *Am. J. Med.* **10**: 53, 1956.
- ⁶ STUART, H. C.: Physical growth and development. In *Nelson's Textbook of Pediatrics*. Philadelphia, W. B. Saunders Co., 1954, p. 45.
- ⁷ WARKANY, J.: Congenital anomalies. *Pediatrics* **7**: 607, 1951.
- ⁸ INGALLS, T. H., CURLEY, F. J., AND PRINDLE, R. A.: Medical progress: Experimental production of congenital anomalies; timing and degree of anoxia as factors causing fetal deaths and congenital anomalies in mouse. *New England J. Med.* **247**: 758, 1952.
- ⁹ BASS, M. H.: Diseases of the pregnant woman affecting the offspring. *Advances Int. Med.* **5**: 15, 1952.
- ¹⁰ GREGG, N. M.: Congenital cataract following German measles in mother. *Tr. Ophth. Soc. Australia* **3**: 35, 1952.
- ¹¹ MURPHY, D. P.: Congenital Malformations: A study of parental characteristics with special reference to the reproductive process. Ed. 2. Philadelphia, J. B. Lippincott Co., 1947, p. 127.
- ¹² CAMPBELL, M.: Genetic and environmental factors in congenital heart disease. *Quart. J. Med.* **18**: 379, 1949.
- ¹³ RUTSTEIN, D. D., NICKERSON, R. J., AND HEALD, F. P.: Seasonal incidence of patent ductus arteriosus and maternal rubella. *Am. J. Dis. Child.* **84**: 199, 1952.
- ¹⁴ FOX, M. J., AND BORTIN, M. M.: Rubella in preg-

- nancy causing malformations in newborn. *J.A.M.A.* **130**: 568, 1946.
- ¹⁵ AYCOCK, E. L., AND INGALLS, T. H.: Maternal disease as principle in the epidemiology of congenital anomalies with review of rubella. *Am. J. M. Sc.* **212**: 366, 1946.
 - ¹⁶ HILL, A. B., AND GALLOWAY, T. M.: Maternal rubella and congenital defects: Data from National Health Insurance Records. *Lancet* **1**: 299, 1949.
 - ¹⁷ BRAWNER, D. L.: Maternal rubella: Results following an epidemic. *J. M. A. Georgia* **44**: 451, 1955.
 - ¹⁸ INGALLS, T. H.: Conference on the effects on offspring of infections during the first trimester of pregnancy. Presented to Graduate Students and Practitioners Conference May 16, 1956, at Children's Hospital, Boston, Mass.
 - ¹⁹ ANDERSON, R. C.: Causative factors underlying congenital heart malformations: I. Patent ductus arteriosus. *Pediatrics* **14**: 145, 1954.
 - ²⁰ MACMAHON, B., McKEOWN, T., AND RECORD, S. G.: The incidence and life expectancy of children with congenital heart disease. *Brit. Heart J.* **15**: 121, 1953.
 - ²¹ INGALLS, T. H.: Personal communication.
 - ²² KRUGMAN, S., WARD, R., JACOBS, K. G., AND LAZAR, M.: Studies on rubella immunization: I. Demonstration of rubella without rash. *J.A.M.A.* **151**: 285, 1953.
 - ²³ ANDERSON, S. G.: Experimental rubella in human volunteers. *J. Immunol.* **62**: 29, 1949.

Goldstein, F., Jenson, W. K., Waldron, J. M., and Duncan, G. G.: **The Relationship between Hypertension and Coronary Occlusion.** *Ann. Int. Med.* **44**: 446 (Mar.), 1956.

It is postulated that hypertension in both sexes is one of several factors involved in atherogenesis, atherosclerosis, and the causation of coronary occlusion and myocardial infarction. Other factors in these processes presumably are diabetes mellitus, certain disturbances in lipid metabolism, and the sex hormones. Until the menopause, women enjoy a fair degree of protection from atherosclerosis and from the accelerating effects of hypertension on atherogenesis. After menopause the number of coronary occlusions associated with, and presumably causally related to, hypertension approaches and eventually equals the number observed in men of similar age. Therefore, the hypertensive factor is presumed to be of equal absolute importance in both sexes. Because other factors operate additionally in the male to accelerate atherogenesis and to cause coronary occlusions, hypertension is of relatively less importance in the male. The positive correlation between hypertension and the incidence of coronary occlusion should be considered, among other factors, in deciding whether a patient with hypertension should receive hypotensive therapy.

WENDKOS

Clinicopathologic Correlations of Renal Biopsies in Hypertension with Pyelonephritis

By JOSEPH C. MERRIAM, M.D., SHELDON C. SOMMERS, M.D.,
AND REGINALD H. SMITHWICK, M.D.

Analysis has been made of the responses to sympathectomy for hypertension and certain other aspects of 120 cases whose renal biopsies showed pyelonephritis as well as arteriolar nephrosclerosis. The sex incidence, mortality, average diastolic blood pressures, and post-operative kidney function tests differed from findings in a larger hypertensive group without pathologic evidence of pyelonephritis.

A STUDY of clinicopathologic correlations of hypertensive patients undergoing sympathectomy at the Massachusetts Memorial Hospitals has recently been reported¹ that was concerned with renal biopsies and clinical follow-up data of the 1- to 9-year period after operation. The majority of the renal biopsies were diagnosed as arteriolar nephrosclerosis. The previous report dealt with this majority. In addition clinically undiagnosed chronic pyelonephritis was found in 13.5 per cent of the total of about 1,700 renal biopsies. In this paper these cases of chronic pyelonephritis are discussed from the viewpoints of clinical findings and prognosis, comparing them with the cases of pure nephrosclerosis previously reported.

MATERIALS AND METHODS

Case records were available of 120 hypertensive patients who had undergone sympathectomy at the Massachusetts Memorial Hospitals between 1947 and 1956, and whose renal biopsy, performed at the time of operation, included the diagnosis of chronic pyelonephritis. Twelve patients had bilateral biopsies, the remaining 108 had a biopsy of only 1 kidney. The biopsies averaged about 6 by 5 by 4 mm., were composed of kidney cortex,

and were removed in a manner previously described by Castleman and Smithwick.² Pathologic alterations of the glomeruli, juxtaglomerular apparatus, tubules, stroma, and blood vessels were recorded for each specimen without knowledge of the patient's identity or status, or whether multiple biopsies had been taken.

Criteria for Diagnoses

The presence of chronic pyelonephritis in these biopsies was recognized by finding irregular scars, dilated tubules containing colloid protein casts, and plasma cells mingled with other leukocytes in the stroma (fig. 1). The most important single criterion was the presence of plasma cells. If regions of dilated tubules containing colloid casts were seen and no plasma cells could be found, a diagnosis of healed pyelonephritis was made (fig. 2). There were 17 such cases in the total group of 120 cases. If pus casts and polymorphonuclear leukocytes were seen in 1 or more tubules, in addition to evidences of chronic pyelonephritis, acute and chronic pyelonephritis was diagnosed; 3 of the 120 cases fell in this group.

These criteria agree well with histopathologic findings reported both in human autopsy and in experimental animal material.³⁻⁵ Bacteriologic cultures of the biopsies were not done.

As reported in the previous paper, the vessels in each biopsy were also studied and the degree of arteriolar sclerosis was graded as grades I, II, or III. Negative arterioles showed no alteration, grade-I arteriolar sclerosis indicated minor localized thickenings of the vessel walls, grade II referred to a thickened wall equal to the diameter of the arteriolar lumen, and grade-III sclerosis meant that the wall thickness exceeded the diameter of the lumen. There were 2 grade-0, 12 grade-I, 96 grade-II, and 10 grade-III cases among the 120 cases. Thus 80 per cent of the cases of chronic or healed pyelonephritis had an associated moderate (grade-II) arteriolar sclerosis.

From the Departments of Pathology and Surgery, Massachusetts Memorial Hospitals and Boston University School of Medicine, Boston, Mass.

Aided by grants from the American Heart Association, the Massachusetts Heart Association, and the Smithwick Foundation.

Presented in part at the International Congress of Clinical Pathology, Brussels, July, 1957.

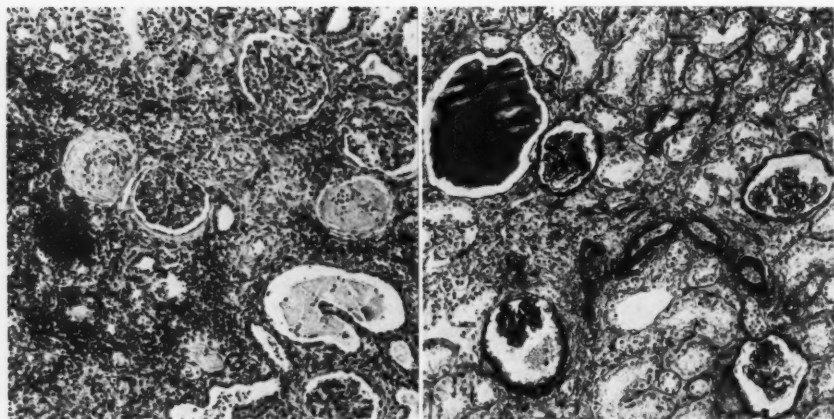


FIG. 1. *Left.* Example of a kidney biopsy with severe chronic pyelonephritis and grade-II arteriolar sclerosis of the vessels in center of the illustration. Parenchymal atrophy, interstitial scar tissue, and abundant leukocytes are evident. H & E, $\times 125$.

FIG. 2. *Right.* Focus of healed pyelonephritis with scarring, renal parenchymal atrophy, and a large colloid cast in a dilated tubule. Grade-II arteriolar sclerosis is shown. This biopsy elsewhere showed acute and chronic pyelonephritis. PAS, $\times 125$.

Twelve patients had bilateral renal biopsies. Five of these patients had the same diagnosis on each biopsy, the other 7 differed either by 1 grade of sclerosis, or by a diagnosis of chronic pyelonephritis on one side, and healed pyelonephritis on the other. For purposes of grouping, these patients were placed in the lower grade of arteriolar sclerosis, and in the group of chronic pyelonephritis. None of the 12 cases with bilateral biopsies was considered to show only a unilateral pyelonephritis.

RESULTS

Of the total 120 patients, 73 or roughly 60 per cent were male. In the larger series of cases that showed arteriolar sclerosis alone, on the other hand, there was a slight preponderance of females, 53.5 per cent.

The age and sex distributions of the 120 cases were as follows: In the age-range of 19 to 29 years, 5 patients, 3 male and 2 female; 29 to 39, 28 patients, 15 male and 13 female. In the age-range 39 to 49, 58 patients, 37 male and 21 female. In the age-range 49 to 60 (the oldest patient was 60 at operation), 29 patients, 18 male and 11 female.

Survival for 5 years after operation for each grade of arteriolar sclerosis accompanying pyelonephritis is charted in figure 3. Over-

all survival at 5 years, for the 75 patients followed that time or longer, was 64 per cent. There were only 3 patients with severe (grade III) arteriolar sclerosis, of whom 1 was alive after 5 years. Twenty patients followed for 10 years or more had a survival rate of 65 per cent at the end of 10 years (fig. 4). The mortality for the hypertensive patients who had the added factor of chronic or healed pyelonephritis was somewhat higher than those in the previous study, in which there was approximately a 90 per cent 5-year survival for all arteriosclerotic groups except grade III.

As in the previous study, a preoperative diastolic blood pressure level was defined as the lowest value obtained in the recumbent patient, and the average pressure was computed for each of the vascular grades I, II, and III. In table 1 are seen the average diastolic pressures, and number of patients used to compute the averages. For comparison, figures from the previous paper are included. By the statistical "t-test," the difference between grade I and II average pressures in the group with pyelonephritis is not significant. The differences in cases

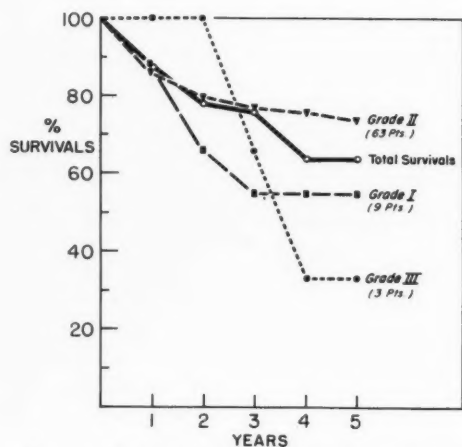


FIG. 3. Relation between grades of arteriolar sclerosis in kidney biopsies and survival.

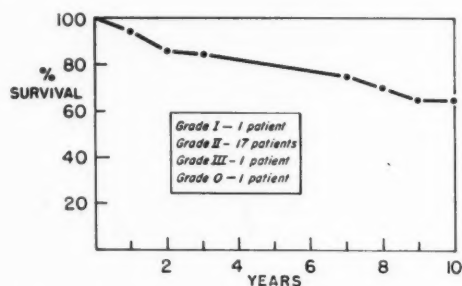


FIG. 4. Survival of cases followed for 10 years after sympathectomy.

with pyelonephritis between grade I or II and III average diastolic pressures, however, are significant. Also for each vascular grade there was a significantly higher average diastolic pressure in the presence of pyelonephritis.

The so-called "Smithwick groups"⁶ offer another method of comparing the biopsy interpretations with the preoperative clinical evaluations. These are 6 groups into which patients are classed, during the preoperative workup, according to factors of age, diastolic blood pressure level and its response to sedation, eyeground observations, renal function, and cardiac and cerebrovascular status. The over-all clinical evaluation then falls into 1 of 6 groups, with the comparatively early and mild cases being assigned to groups

TABLE 1.—Average Diastolic Blood Pressures in mm. Hg

Grade	Arteriolar sclerosis only	Pyelonephritis and arteriolar sclerosis
I	100.3 (100 cases)	111.5 (12 cases)
II	109.6 (100 cases)	115.3 (96 cases)
III	122.1 (29 cases)	133.4 (10 cases)

TABLE 2.—Clinical Hypertensive Groups Compared with Kidney Biopsy

Pyelonephritis and arteriosclerosis	Group					
	1	2	3	4	5	6
Grade I (12 cases)	0	2	5	4	1	0
Grade II (95 cases)	5	11	27	36	7	9
Grade III (10 cases)	1	0	3	3	0	3
Total 117 cases	6	13	35	43	8	12

1 and 2, and the most severe and advanced hypertensive disease to group 6. In table 2 are presented data of 117 of the cases of pyelonephritis, comparing the preoperative Smithwick group with the grade of arteriolar sclerosis.

As compared to the results of analysis of the noninfected nephrosclerotic cases in the previous paper, the following distinction may be pointed out. More than half of the 117 cases of chronic pyelonephritis fell into the more "severe" groups of 4, 5, and 6, whereas only one quarter of the purely nephrosclerotic cases were in groups 4, 5, 6.

Postsympathectomy Follow-up

Eighty-three patients have been followed for 5 years or more after sympathectomy. Of these, 50 have had rather thorough follow-up studies from 1 to 10 years after operation. We wish to report some of the follow-up studies, and to compare them with studies reported in the previous paper.

The postoperative response of diastolic blood pressure has been analyzed according to Smithwick's criteria.^{6,7} The 50 pyelonephritic patients in this respect did about as well as the pure nephrosclerotic group, since approximately one third of the pyelonephritic and the nephrosclerotic groups each fell into grades I to III of postsympathectomy response.

Grading of retinal vascular changes (Keith-Wagener) was compared before and after

TABLE 3.—*Phenolsulfonphthalein Excretion (per cent)*

	Normal	Preoperative			Postoperative		
		Sl.	Impaired Mod.	Mked.	Same	Improved	Worse
Nephrosclerosis (265 cases).....	64	25	7	4	10	69	18
Chronic pyelonephritis (50 cases).....	52	52	8	14	54	18	28

operation for both the pyelonephritic and the pure nephrosclerotic groups of patients. The incidence of hypertensive retinopathy of grades III and IV was 45 per cent in the pyelonephritis series as opposed to 24 per cent in the nephrosclerotic group. After sympathectomy the pyelonephritic series showed an incidence of 46 per cent of improvement in the eyegrounds, which compares almost exactly with the figure of 48 per cent improvement reported previously for the nephrosclerotic series.

Thus both series did roughly equally well postoperatively with respect to lowering of blood pressure and improvement in eyegrounds.

An attempt was also made in the previous paper to assess kidney function in terms of the phenolsulfonphthalein test before and after operation. Because of the relatively few (50) cases of pyelonephritis that were observed for 5 years, all of the cases were pooled, and the data obtained compared to the total data of the nephrosclerotic series.

As compared with the nephrosclerotic series, the pyelonephritic series showed a trend toward greater severity of renal impairment in more patients, and a less frequent improvement of the renal function after sympathectomy.

Also in contrast to the series of nephrosclerotic patients, in which only 3 patients had nonprotein nitrogen serum values of over 45 mg. per cent preoperatively and all improved after sympathectomy, in the pyelonephritic series 10 out of 120 patients had serum nonprotein nitrogen levels of over 45 mg. per cent. Only 1 of these patients improved postoperatively, and 7 died of uremia within 2 years.

Thirty-three patients with hypertension and pyelonephritis have died altogether, 12

of uremia, 10 of cerebrovascular accidents, 6 of myocardial infarct, and 1 each of ruptured aorta, cancer of the bladder, acute enteritis, and congestive heart failure. Autopsies were performed in 7 cases at the Massachusetts Memorial Hospitals. Studies of their kidneys post mortem showed good general agreement between the biopsy and the autopsy kidney findings, except in 1 case, in which no obvious stigmata of chronic or healed pyelonephritis, or of arteriolar sclerosis, were found at autopsy in a woman previously diagnosed by biopsy as having chronic pyelonephritis and grade I arteriolar sclerosis (figs. 5 and 6).

DISCUSSION

This investigation was undertaken to see whether there were any differences in the clinical evaluation, course, and prognosis of 2 series of sympathectomized hypertensive patients, one group in which renal biopsies showed only arteriolar nephrosclerosis, and the other group with arteriolar sclerosis and the additional factor of chronic pyelonephritis. It must be emphasized again that these cases of pyelonephritis were diagnosed pathologically by biopsy, and that practically none of these patients had been previously recognized clinically as having chronic pyelonephritis. Exhaustive investigation into their past histories was not done, but the impression was gained from the available records that few of these patients were aware of any previous episode of kidney infection.⁸

In comparing the 2 series of noninfected and infected cases, an obvious associated factor in the study is the much larger proportion in the nephrosclerotic group of cases diagnosed as grade-I nephrosclerosis. The total group of pure nephrosclerotic cases represented nearly an equal mixture of grade-I

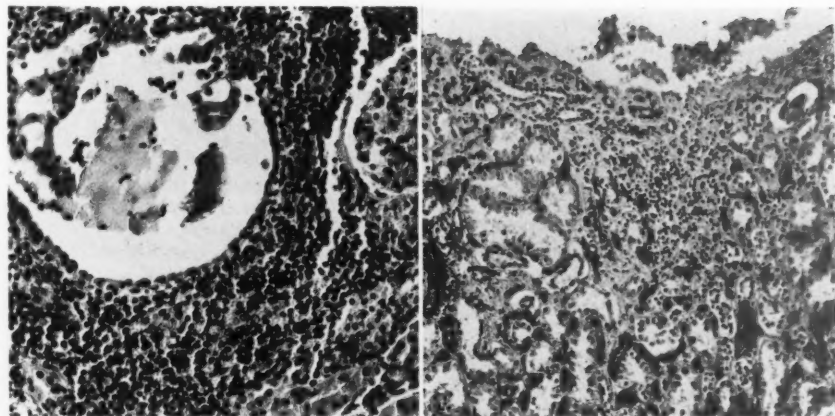


FIG. 5. *Left.* Portion of kidney biopsy, with a dilated tubule containing colloid material and leukocytes, as well as an interstitial leukocytic infiltration including plasma cells. Grade-I arteriolar sclerosis was present. H & E, $\times 750$.

FIG. 6. *Right.* Autopsy specimen of kidney, from the same 42-year-old woman as figure 5, obtained the same year as the biopsy, following death from cerebral thrombosis. The shallow superficial scar shown was the only suggestion of previous pyelonephritis. H & E, $\times 125$.

arteriolar sclerosis with much smaller numbers of the other grades, whereas 80 per cent of the pyelonephritic cases were classed as grade-II arteriolar sclerosis. This disparity might influence differences already pointed out, such as the increased mortality with pyelonephritis, the relatively larger number of patients present in the less favorable Smithwick clinical groupings preoperatively, the increased incidence of higher grades of retinopathy, or the decreased likelihood of postoperative improvement in impaired renal function in the pyelonephritic groups, as compared to the nephrosclerotic group. Nevertheless, the factor of differing grades of vascular sclerosis between grades I and II alone was shown in the previous paper to have been of little importance in terms of the survival, postoperative response, eyeground changes, and phenolsulfonphthalein excretion.

That a slight majority of males over females was found in the chronic pyelonephritis group is surprising, in view of the fact that chronic pyelonephritis is supposed to be much commoner among females than males.

The pathogenetic relationship of the pye-

lonephritis to the hypertension is obscure, and this paper does not pretend to illuminate the mystery. Lately there has been renewed interest in the possibility that unilateral kidney infection or ischemia may cause hypertension that is curable by nephrectomy. Smith⁹ estimated that less than 2 per cent of all patients with diastolic hypertension can be helped by renal surgery. One patient of the 120 undergoing sympathectomy also had a removal of an atrophic, chronically infected kidney, and 4 years later showed a grade-I operative response with reduction in the diastolic blood pressure of 20 mm. Hg or more, and below 90 mm. This patient's biopsy from the opposite kidney showed chronic pyelonephritis and arteriolar sclerosis, grade II. Four other atrophic kidneys were removed in the series, but these patients had incomplete follow-up studies.

SUMMARY

Renal biopsies from 120 cases of hypertension taken during sympathectomy were diagnosed pathologically partly as chronic pyelonephritis. Clinical comparisons were made with a larger series of hypertensive patients

whose biopsies did not demonstrate pyelonephritic infection. The pyelonephritic series had a somewhat increased mortality, significantly higher average diastolic blood pressures for the same grades of arteriolar sclerosis, and did not show as frequent improvement of impaired kidney function post-operatively as the purely nephrosclerotic group. Approximately one third of each series responded with a lowering to normal levels of the diastolic blood pressure after sympathectomy, and nearly one half showed a postoperative improvement in the hypertensive retinopathy.

SUMMARIO IN INTERLINGUA

Biopsias renal ab 120 casos de hypertension, obtenite durante sympathectomia, supportava in parte le diagnose pathologic de pyelonephritis chronie. Comparationes clinic esseva facite con un plus grande serie de patientes hypertensive in qui le biopsias non demonstrava le presentia de infection pyelonephritie. Le serie pyelonephritie monstrava un leve augmento del mortalitate e significativemente plus alte valores medie del pression de sanguine diastolic pro le mesme grado de sclerosis arteriolar sed attingeva minus frequentemente un melioration del dysfunction renal post le operation que le serie purmente nephrosclerotic. Circa un tertio del patientes in ambe gruppos respondeva al sympathectomia per le redescendita a nivellos normal del pression de sanguine

diastolic, e quasi un medietate monstrava un melioration post-operatori in le retinopathia hypertensive.

REFERENCES

1. SALTZ, M., SOMMERS, S. C., AND SMITHWICK, R. H.: Clinico-pathologic correlations of renal biopsies from essential hypertensive patients. *Circulation* **16**: 207, 1957.
2. CASTLEMAN, B., AND SMITHWICK, R. H.: The relation of vascular disease to the hypertensive state, based upon a study of renal biopsies from 100 hypertensive patients. *J.A.M.A.* **121**: 1256, 1943.
3. MALLORY, G. K., CRANE, A. R., AND EDWARDS, J. E.: Pathology of acute and of healed experimental pyelonephritis. *Arch. Path.* **30**: 330, 1940.
4. WEISS, S., AND PARKER, F., JR.: Pyelonephritis: Its relation to vascular lesions and to arterial hypertension. *Medicine* **18**: 221, 1939.
5. DE NAVASQUEZ, S.: Further studies in experimental pyelonephritis produced by various bacteria, with special reference to renal scarring as a factor in pathogenesis. *J. Path. & Bact.* **71**: 27, 1956.
6. SMITHWICK, R. H.: Surgical Measures in Hypertension, Publication 61, American Lecture Series, Monograph in American Lectures in Surgery. Springfield, Ill., Charles C Thomas, 1951.
7. —: Hypertensive cardiovascular disease: The effect of thoracolumbar splanchnicectomy on mortality and survival rates. *J.A.M.A.* **149**: 1611, 1951.
8. SAPHIR, O., AND TAYLOR, B.: Pyelonephritis lenta. *Ann. Int. Med.* **36**: 1017, 1952.
9. SMITH, H. W.: Unilateral nephrectomy in hypertensive disease. *J. Urol.* **76**: 685, 1956.



Corrected Transposition of the Great Vessels, Atrioventricular Heart Block, and Ventricular Septal Defect

A Clinical Triad

By WELDON J. WALKER, COLONEL, M.C., DENTON A. COOLEY, M.D.,
DAN G. McNAMARA, M.D., AND ROBERT H. MOSER, MAJOR, M.C.

Three cases with the triad of ventricular septal defect, atrioventricular heart block, and corrected transposition of the great vessels are presented. In each instance the patient successfully underwent open heart surgery on the pump-oxygenator for closure of the ventricular septal defect. A review of the literature suggests a frequent association of these 3 congenital anomalies. In our experience atrioventricular heart block is rarely encountered with simple ventricular septal defect. The finding of atrioventricular heart block in a patient with an interventricular septal defect warrants consideration of an associated corrected transposition of the great vessels.

CORRECTED transposition of the great vessels is a rare anomaly in which the root of the aorta arises anterior to the pulmonary artery, yet each major vessel receives blood from its "correct" ventricle, (the aorta from the left ventricle, the pulmonary artery from the right). As illustrated in figure 1, the main pulmonary artery fails to arch in front of the aorta in the normal manner, and the left pulmonary artery passes behind the ascending aorta. Figure 2 illustrates the medial displacement of the cardiac catheter as it passes through the main pulmonary artery in corrected transposition. In complete transposition of the great vessels the position of the major trunks is similarly altered but they originate from reversed ventricles, the aorta from the right, and the pulmonary artery from the left ventricle.

We are reporting 3 cases that represent combinations of defects that have been reported previously but whose association has not been stressed, namely "corrected transposition" of the aorta and pulmonary ar-

tery, ventricular septal defect, and congenital atrioventricular heart block. The diagnosis was confirmed in all patients at open heart surgery on the pump-oxygenator. All demonstrated a gratifying clinical response after closure of their ventricular septal defects.

CASE REPORTS

Case 1. A 10-month-old white boy was the product of a gestation that was unremarkable except for fetal bradycardia (70 to 80/minute) detected during the seventh month of pregnancy. At 11 weeks of age the infant was admitted to Brooke Army Hospital following treatment for pneumonia and congestive failure at another hospital. Examination revealed a small, feeble baby with a pulse rate of 64 and a respiratory rate of 60, but without cyanosis. There was severe pectus excavatum. Oxygen saturation on an ear oximeter reading was 97 per cent. Cardiac fluoroscopy revealed increased pulmonary vascularity and combined ventricular enlargement. An electrocardiogram revealed complete atrioventricular block (fig. 3).

The infant did poorly, with recurrent congestive failure and repeated pulmonary infections. Cardiac catheterization on October 23, 1956, showed a right-to-left shunt at the ventricular level. The pressure in the right ventricle was 65/0 mm. Hg and 65/20 in the pulmonary artery. Systemic arterial blood was 95 per cent saturated. On November 27, 1956, there was clinical and radiographic evidence of atelectasis of the left lower lobe.

Open heart surgery on the pump-oxygenator

From the Cardiovascular Service, Brooke Army Hospital, Fort Sam Houston, Texas; the Cardiac Clinic, Texas Childrens' Hospital, and the Departments of Surgery and Pediatrics, Baylor University, College of Medicine, Houston, Tex.

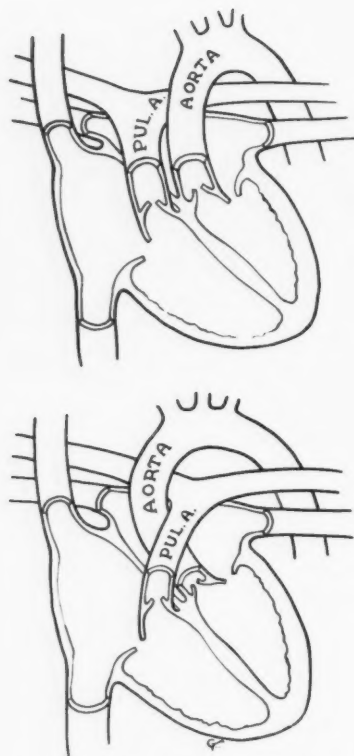


FIG. 1. Schematic diagram contrasting the relationship between the great vessels in corrected transposition (*Top*) and the normal heart (*Bottom*). In both instances the pulmonary artery and aorta receive blood from the "correct" ventricle. Drawings by George Thomas.

was performed at the Texas Children's Hospital on December 20, 1956. Exploration revealed a corrected transposition and a ventricular septal defect 2 cm. in diameter located high in the septum behind the right atrioventricular valve. This was closed by figure-of-8 sutures. The patient tolerated the procedure well and had an uneventful postoperative course. At the time of discharge 10 days after surgery, the murmur was inaudible. Continued improvement was noted on follow-up examination 2 months later.

Case 2. This 13-year-old white girl was the product of a gestation complicated by repeated episodes of threatened abortion during the first trimester. Cyanosis was observed in the immediate postnatal period and a murmur was detected at 3 months of age. In the first 3 years, there were recurring episodes of respiratory infection, including 5 bouts of pneumonia in 1 year. During this period the patient manifested continuous cy-

anosis and had frequent "attacks" characterized by syncope and more severe cyanosis.

At age 8 cardiac catheterization was thought to demonstrate a single ventricle with transposition of the great vessels. Arterial oxygen saturation was 86 per cent. During the following 4 years her general condition improved. She was no longer cyanotic and had increased exercise tolerance.

Physical examination revealed a child of slender build, weighing 56½ pounds. There was questionable cyanosis of the fingers and toes, with slight clubbing. The ventricular rate was 60 per minute. The electrocardiogram showed complete heart block (fig. 4). Fluoroscopy showed marked cardiomegaly with a globular configuration of the heart and increased pulmonary vascularity without hilar dance. The pulmonary artery segment was not prominent (fig. 5). An oximeter reading was 95 per cent.

Cardiac catheterization revealed a large ventricular septal defect with predominantly left-to-right shunt. There was an increase from 61 per cent to 80 per cent saturation of blood from the right atrium to the right ventricle; femoral arterial blood saturation was 95 per cent; right ventricular pressure was 115/10 mm. Hg.

At operation there was corrected transposition of the great vessels and a 3-cm. defect high in the membranous septum. The defect was repaired. The patient tolerated the procedure well and there was a demonstrable reduction in pulmonary artery pressure after closure of the defect. The patient has continued to do well after discharge from the hospital.

Comment. The progressive decrease in cyanosis and improvement in exercise tolerance during several years prior to surgery will be the subject of a later report following postoperative catheterization, since it raises the question of possible cardiac surgery at a later date in cyanotic children with septal defects. In the past cyanosis has been considered to represent an irreversible process of increased pulmonary vascular change. This child had well-documented persistent cyanosis until 8 years of age. Then her cyanosis virtually disappeared and at 12 years of age, pulmonary vascular resistance had diminished to the point that pulmonary blood flow exceeded systemic flow. The child appeared to be benefited by closure of her ventricular septal defect.

Case 3. This 6-year-old white boy had a known cardiac murmur at 5 weeks of age. He was dyspneic on exertion. Physical examination revealed him to be well developed and nourished and without cyanosis. There was slight bulging of the left anterior chest wall. The electrocardiogram revealed incomplete atrioventricular block with intermittent dropped beats (fig. 6). Roentgenograms and fluoroscopy revealed an enlarged globu-

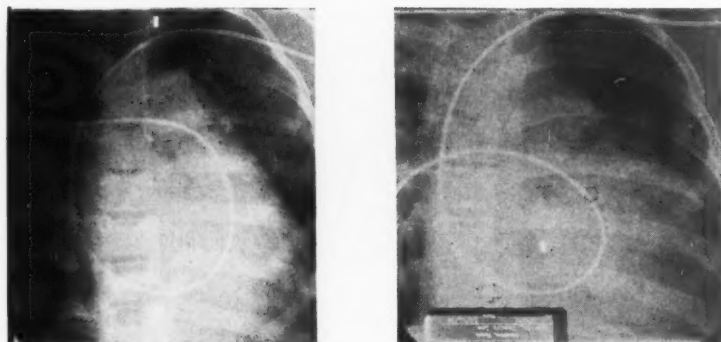


FIG. 2. Position of the cardiac catheter in the normal heart (*Left*) compared with that in corrected transposition (*Right*). In each case the catheter tip lies in the right pulmonary artery. The more medial position of the pulmonary outflow tract in corrected transposition can be seen by the relatively greater distance from the catheter to the left border of the cardiac silhouette.

lar heart with increased pulmonary vascular markings. Cardiac catheterization showed a left-to-right shunt at the ventricular level and pulmonary hypertension (90/50 mm. Hg). On November 27, 1956, the ventricular defect was closed. The patient was noted to have corrected transposition of the great vessels. During the early postoperative period transient atrioventricular dissociation was observed. On the third postoperative day the patient developed abdominal distention and liver enlargement, but there was prompt improvement following the administration of digitalis and mercurial diuretics. The patient was discharged from the hospital in good condition on December 16, 1956.

DISCUSSION

Corrected transposition is a rare anomaly. Abbott in 1936¹ reported a total of 6 cases in her series of 1,000 congenital defects. Considerable difference of opinion has been expressed by anatomists and embryologists concerning the nature and evolution of this defect. This is rather extensively reviewed by Bremer,² Harris and Farber,³ Lev and Saphir,⁴ and Cardell.⁵ It must be understood that the term corrected transposition refers to a functional "correction." Despite the varieties of transposition and inversion that the great vessels, atria, and ventricles may undergo, the end result is that the aorta receives oxygenated blood and the pulmonary artery receives systemic venous blood. Cardell⁵ cites 8 different anatomic combinations that may occur in corrected transposition.

In the usual form of corrected transposition the aorta arises anterior and to the

left of the pulmonary artery. The left ventricle is continued upward and anteriorly into a short infundibular portion from which the aorta arises. There is no infundibular portion of the right ventricle and the pulmonary artery arises directly from the base of this ventricle in close proximity to the usual location of membranous ventricular septal defects. As pointed out by Edwards,⁶ "The architecture of the right ventricle resembles that of a normal left ventricle and, conversely, that of the left-sided ventricle resembles the architecture of a normal right ventricle. The right atrioventricular valve in corrected transposition resembles a normal mitral valve in its structure, whereas the left atrioventricular valve structurally resembles a normal tricuspid valve." The left-sided tricuspid valve is frequently deformed and incompetent in corrected transposition. The aorta and pulmonary artery arise side by side without the normal spiraling and the left pulmonary artery passes posterior to the ascending aorta. Functionally corrected transposition is compatible with normal longevity. It is the frequently associated anomalies that cause the morbidity and mortality in this disease.

In 1956 Cardell⁵ reviewed the literature on corrected transposition and reported a case with corrected transposition, ventricular septal defect, and 2:1 atrioventricular block. In a review of 18 cases of corrected transposition from the literature he reported an

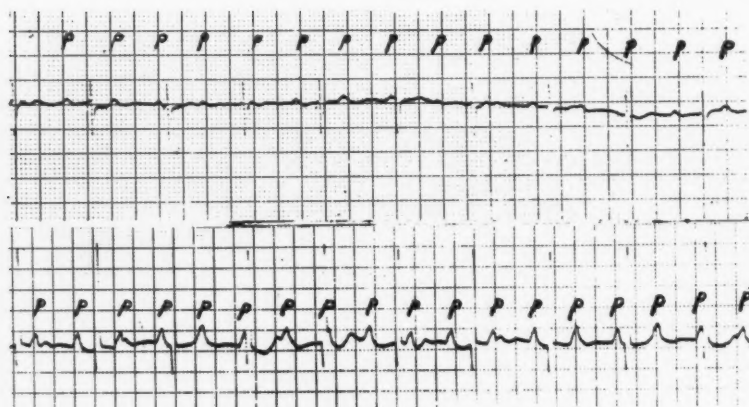


FIG. 3. *Top.* Lead I of the electrocardiogram of case 1. Regular atrial rate 157 per minute, regular ventricular rate 93 per minute. The absence of any consistent time relationship between the regular P waves and QRS complexes indicates complete atrioventricular block.

FIG. 4. *Bottom.* Lead II of electrocardiogram of case 2. Regular atrial rate 143 per minute, regular ventricular rate 79 per minute. The absence of any consistent time relationship between the regular P waves and QRS complexes indicates complete atrioventricular block.

equal sex distribution. Duration of life varied from 9 days to 46 years (average 14 years). Septal defects (atrial or ventricular or both) were especially common, and in only 4 cases were both septa intact. Only 2 cases had no associated anatomic defects, and 1 of these had complete heart block. Of the 18 cases from the literature with adequate records, 3 had complete heart block and a fourth 2:1 A-V block. Helmholz et al.,⁷ whose paper was not included in Cardell's review, reported 1 patient with complete heart block who demonstrated corrected transposition at catheterization. In addition these authors reported 6 cases of corrected transposition studied pathologically. Three of these had associated ventricular septal defects, 5 had defects of the left atrioventricular valve, 3 had anomalous insertion of the chordae, and 2 had a left-sided Ebstein type of malformation. None of the 6 cases was reported to have atrioventricular block but this was a pathologic rather than a clinical study and this information may not have been available. Donoso et al.⁸ also reported a case not included in Cardell's review (case 1 in their report), who had congenital complete heart block, corrected transposition, ventricular septal defect, and atresia of the mitral valve.

In 1933 Yater et al.⁹ gathered 44 examples

of congenital atrioventricular heart block from the literature and reported 1 case of congenital complete atrioventricular block with ventricular septal defect studied by serial sections through the conduction system. Of the 44 cases with atrioventricular block, 29 had associated ventricular septal defects. Corrected transposition was not mentioned in this paper. However, a review of figure 4 shows that in the case they reported the aorta arose anteriorly, and we believe it also represents an example of the triad. Yater¹⁰ and Edwards¹¹ have reviewed the published photographs and agree that this is probably true.

Keith et al.¹² reviewed 44 necropsied cases of complete transposition of the great vessels. They found patent foramen ovale in all, patent ductus arteriosus in 25, ventricular septal defect in 18, and atrial septal defects in 2. Electrocardiograms were taken in 30 cases but no comment was made on the presence of conduction defects. Kjellberg et al.¹³ presented 8 cases of complete transposition, 3 with associated ventricular septal defects, 3 with patent foramen ovale, and 1 with atrial septal defect. Electrocardiograms were done in 7 instances, but conduction defects were not remarked upon. This suggests that complete transposition of the great vessels is less

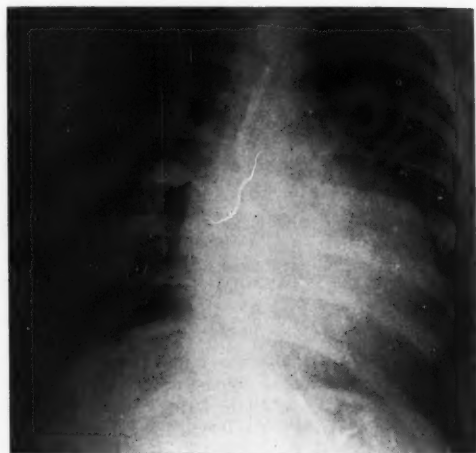


FIG. 5. Roentgenogram of the chest in case 2. The heart is enlarged and globular with accentuated vascular markings and tapering narrow base. This appears to be the characteristic configuration of the heart in corrected transposition with ventricular septal defect. A roentgenogram of case 3 was identical in appearance. Case 1 failed to show this configuration, apparently due to displacement of the heart secondary to severe pectus excavatum.

commonly associated with atrioventricular block than is corrected transposition. It is obvious that in complete transposition, survival beyond the immediate postnatal period necessitates the presence of a shunt to permit some of the oxygenated blood to perfuse the systemic vessels. This is not essential for survival with corrected transposition. However, it appears that ventricular septal defects are equally common in both conditions.

Although the association of congenital heart block with ventricular septal defect has been stressed in the past, it should be noted that in the 200 cases of interventricular septal defect reviewed by Brown¹⁴ no cases of congenital heart block were found. Downing and Goldberg¹⁵ reviewed 100 cases of ventricular septal defects. Electrocardiograms were done in 91. There were no instances of complete heart block, although incomplete atrioventricular block was found in 3. Kjellberg et al.¹⁶ cite 54 cases of ventricular septal defects with no associated complete heart block although 4 presented delayed atrioventricular conduction. In nei-

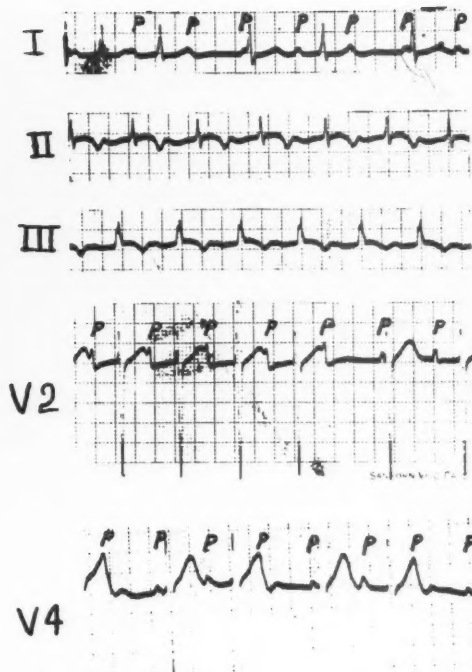


FIG. 6. Electrocardiogram of case 3. Tracing shows incomplete atrioventricular heart block with intermittent dropped ventricular beats. In leads I, V₂ and V₄, there are uniform QRS complexes, which are irregular in rate and less frequent than the P waves. In leads II and III the P-R interval is prolonged (0.28 second) but all P waves are followed by QRS complexes.

ther series was corrected transposition reported.

Of 69 patients operated at the Texas Children's Hospital for closure of ventricular septal defect, 3 had associated corrected transposition of the great vessels. All of these had associated congenital atrioventricular block; this was complete in 2 instances and incomplete in 1. One additional patient had transposition of the great vessels with a common ventricle; this patient did not manifest atrioventricular block. Of the remaining 65 patients with ventricular septal defect and normal origin of the great vessels none had complete atrioventricular block, only 4 manifested incomplete atrioventricular block, and in only 1 of these did the P-R interval exceed 0.20 second. Lillehei¹⁷ has also observed the association of ventricular septal defect,

corrected transposition of the great vessels, and complete atrioventricular block. Whereas acquired atrioventricular block may be a serious complication of open cardiac surgery for repair of ventricular septal defects, experience indicates that congenital atrioventricular block is usually well tolerated.

SUMMARY

Three cases with the triad of atrioventricular heart block associated with ventricular septal defect and corrected transposition of the great vessels are reported. All cases underwent open heart surgery on the pump-oxygenator for closure of their ventricular septal defect. A review of the literature suggests that atrioventricular heart block is associated more frequently with corrected transposition of the great vessels and ventricular septal defect than with isolated ventricular septal defect or with other congenital anomalies. The finding of congenital atrioventricular block in association with ventricular septal defect should alert the observer to search for corrected transposition of the great vessels.

ADDENDUM

Dr. Howard B. Burchell of the Mayo Clinic has also observed 3 cases of this syndrome and believes that there is evidence to support the viewpoint that there is sufficient consistency in the association of the finding of heart block, corrected transposition, and ventricular septal defect to constitute a clinical syndrome.

SUMMARIO IN INTERLINGUA

Es reportate 3 casos del triada de bloco cardiac atrioventricular con defecto ventriculo-septal e corrigite transposition del grande vasos. Omne le casos esseva subiecte a chirurgia cardiac aperte, con le oxygenator-pumpa, pro effectuar clausura del defecto ventriculo-septal. Un revista del litteratura pare indicar que bloco cardiac atrioventricular es associate plus frequentemente con transposition corrigite del grande vasos e defecto ventriculo-septal que con defecto ventriculo-septal sol o que con altere anomalias congenite. Le constatation de congenite bloco atrioventricular in association con defecto ventriculo-septal deberea alarmar le

observator a cercar transposition corrigite del grande vasos.

REFERENCES

1. ABBOTT, M. E.: *Atlas of Congenital Cardiac Disease*. New York, American Heart Association, 1936, p. 58.
2. BREMER, J. L.: Transposition of the aorta and pulmonary artery, an embryological study of its cause. *Arch. Path.* **34**: 1016, 1942.
3. HARRIS, J. S., AND FARBER, S.: Transposition of great cardiac vessels with special reference to the phylogenetic theory of Spitzer. *Arch. Path.* **28**: 427, 1939.
4. LEV, M., AND SAPHIR, O.: A theory of transposition of the arterial trunks based on the phylogenetic and ontogenetic development of the heart. *Arch. Path.* **39**: 172, 1945.
5. CARDELL, B. S.: Corrected transposition of the great vessels. *Brit. Heart J.* **18**: 186, 1956.
6. EDWARDS, J. E.: Differential diagnosis of mitral stenosis. A clinicopathologic review of simulating conditions. *Lab. Invest.* **3**: 89, 1954.
7. HELMHOLTZ, H. F., DAUGHERTY, G. W., AND EDWARDS, J. E.: Cardiac clinics. CXLV. Congenital "mitral" insufficiency in association with corrected transposition of the great vessels; report of probable clinical case and review of six cases studied pathologically. *Proc. Staff Meet., Mayo Clinic* **31**: 82, 1956.
8. DONOSO, E., BRAUNWALD, E., JICK, S., AND GRISHMAN, A.: Congenital heart block. *Am. J. Med.* **20**: 869, 1956.
9. YATER, W. M., LYON, J. A., AND McNABB, P. E.: Congenital heart block, review and report of the second case of complete heart block studied by serial sections through the conduction system. *J.A.M.A.* **100**: 1831, 1933.
10. —: Personal communication.
11. EDWARDS, J. E.: Personal communication.
12. KEITH, J. D., NEILL, C. A., VLAD, P., ROWE, R. D., AND CHUTE, A. L.: Transposition of the great vessels. *Circulation* **7**: 830, 1953.
13. KJELLBERG, S. R., MANNHEIMER, E., RUDHE, U., AND JONSSON, B.: *Diagnosis of Congenital Heart Disease*. Chicago, The Year Book Publishers, Inc., 1955, p. 569.
14. BROWN, J.: *Congenital Heart Disease*. London, Staples Press, 1951.
15. DOWNING, D. F., AND GOLDBERG, H.: Cardiac septal defects. I. Ventricular septal defect. Analysis of 100 cases studied during life. *Dis. Chest* **29**: 475, 1956.
16. KJELLBERG, S. R., MANNHEIMER, E., RUDHE, U., AND JONSSON, B.: *Diagnosis of Congenital Heart Disease*. Chicago, The Year Book Publishers, Inc., 1955, p. 254.
17. LILLEHEI, C. W.: Personal communication.

Reliability of Electrocardiographic Diagnosis of Left Ventricular Hypertrophy

By ARTHUR SELZER, M.D., CARL L. EBNOTHER, M.D., PETER PACKARD, M.D.,
ARTHUR O. STONE, M.D., AND JOHN E. QUINN, M.D.

This is an electrocardiographic-pathologic study in which the presence and degree of left ventricular hypertrophy found at necropsy were correlated with electrocardiographic abnormalities suggesting the diagnosis of left ventricular hypertrophy. The nonspecificity of some electrocardiographic findings is emphasized by the occasional erroneous diagnosis of left ventricular hypertrophy.

THE diagnosis of ventricular hypertrophy ranks high in importance among the various clinical applications of electrocardiography, because electrocardiographic alterations may exist without other clinical signs of hypertrophy. Such early diagnosis of ventricular hypertrophy may be of great practical import, since the application of many newer medical and surgical methods of therapy often depends on the presence or absence of ventricular hypertrophy.

Although a number of criteria for the electrocardiographic diagnosis of left ventricular hypertrophy has been recommended by various investigators,¹⁻⁸ a recent survey by questionnaire⁹ revealed some hesitation on the part of several experts in accepting a strictly defined set of diagnostic criteria.

Many excellent studies of clinical and electrocardiographic correlation of left ventricular hypertrophy have been made. However, relatively little information is available concerning autopsy verification of such studies. In a recent report, Scott et al.¹⁰ examined a series of electrocardiograms from patients in whom autopsies showed evidence of left ventricular hypertrophy, in order to assess the reliability of electrocardiographic criteria suggested by various workers. These authors, however, investigated only the positive side

of the correlation and made no attempt to explore the possibility of incorrect, false positive electrocardiographic diagnoses. The current study was undertaken to provide additional electrocardiographic-anatomic correlation and to investigate the negative as well as the positive aspects of the problem.

MATERIAL AND METHODS

The study was based upon routine material from the Electrocardiographic department of the Veterans Administration Hospital, San Francisco, and the routine autopsy material from the files of its Department of Pathology, during the period of 1948 to 1955. All electrocardiographic tracings were taken with the Cambridge string-galvanometer electrocardiograph with photographic records. Conventional speed (25 mm. per second) and sensitivity (1 mv. per cm.) were used throughout and all measurements were corrected for minor deviations in string sensitivity. Twelve-lead electrocardiograms were taken routinely, including 3 standard extremity leads, 3 augmented unipolar extremity leads, and 6 precordial unipolar leads. Autopsies were performed with a uniform technique, the gross examination of the heart being carried out according to Saphir's recommendations.¹¹ The hearts were weighed after postmortem clots and the great vessels had been removed.

The study was organized as follows: (1) All patients on whom necropsy was performed and who had had an electrocardiogram taken during life within the period of 1948 to 1955 constituted the basic group of 550 cases. (2) The electrocardiographic criteria for left ventricular hypertrophy were collected from the literature and were grouped into 3 classes (table 1). (3) The 550 electrocardiographic tracings were reviewed by 2 observers, who selected records in which criteria for left ventricular hypertrophy were met. These observers had had no knowledge of the necropsy

From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, Stanford University School of Medicine, San Francisco, Calif.

Supported by a grant from the San Mateo County Heart Association.

TABLE 1.—*Electrocardiographic Criteria for Left Ventricular Hypertrophy*

Author	Voltage	Ventricular activation time	ST-T	Others
Gubner ¹	R ₁ +S ₃ over 25 mm.		ST ₁ depr. T ₁ lowered	
Katz ³			S-T ₁ depr. T ₁ low T _{V5} low, inv.	Left axis deviation with S ₂
Schack ⁷	aV _R neg, over 14 mm. aV _L : R over 12 mm. aV _F : R over 19 mm.*			
Goldberger ⁵	R _{aVL} over 13 mm. R _{aVF} over 20 mm.*		"Strain" ST, T in aV _L or aV _F *	Long QT in aV _L or aV _F *
Goulder ⁸	R _{aVL} over 11 mm.		T : R in aV _L less than 10%	
Noth ⁴		over 0.04 sec. for R waves, over 0.05 sec. for qR waves		
Wilson ²	R _{V1} 1 mm. or less S _{V1} 24 mm. or more R _{V5} 33 mm. or more R _{V6} 26 mm. or more	0.05 sec. or more in V ₅ or V ₆ QRS .10 to .11 sec.	T inverted in V ₅ or V ₆	Transitional zone to the left
Sokolow ⁶	R _{VaL} over 11 mm. R _{VaF} over 19 mm.* R _{V5} over 26 mm. R _{V6} over 26 mm. S _{V1} +R _{V5, 6} over 35 mm.	0.05 sec. or more in V ₅ or V ₆	T upr. in aV _R S-T depressed in aV _L , aV _F ,* V ₅ or V ₆ ; T low or inv. aV _L , aV _F ,* V ₅ , V ₆ ; R : T ratio 10 to 1 or more, V ₅ or V ₆	R/S in V ₅ to R/S in V ₁ over 100

*In the presence of vertical position.

findings and disregarded the original interpretations of the electrocardiograms. A single criterion in the classes of increased voltage and prolonged ventricular activation time (table 1) was acceptable as a basis for the electrocardiographic diagnosis of left ventricular hypertrophy. However, abnormalities of the ST-T part of the ventricular complex were not considered specific enough to constitute the sole basis for a diagnosis of left ventricular hypertrophy and were only accepted in combination with 1 or more criteria from the other classes. (4) Of all records in which criteria for left ventricular hypertrophy were met, a smaller group was selected wherein the diagnosis was thought to be uninfluenced by any other fac-

tor. This final group of 108 cases was obtained by eliminating all records in which the following conditions existed: (a) those in which an unduly long time had elapsed between the electrocardiographic examination and death; (b) those wherein a new condition may have developed after the last electrocardiographic examination that could have affected the postmortem diagnosis of left ventricular hypertrophy; (c) records showing electrocardiographic evidence of myocardial infarction, recent or old; (d) records with tachycardia (over 110 per minute) or complete heart block; (e) records of patients with obvious electrolyte disturbance; (f) records showing possible drug effect: an arbitrary 2-week limit had been

set between the last dose of a cardiac drug (digitalis, quinidine, or procaine amide) and an acceptable electrocardiogram. (5) The autopsy protocols of these 108 patients were carefully studied and the following data recorded: the total heart weight; thickness of each ventricular wall; the examiner's notation regarding chamber enlargement; gross or microscopic evidence of infarction or scarring; evidence of other myocardial or pericardial disease; the cause of death and anatomic diagnoses; the patient's weight and height; any other factor that may have had some bearing on the problem.

In considering the anatomic criteria for the presence or absence of left ventricular hypertrophy, it was decided to rely exclusively upon the total cardiac weight. The tables of Zeek¹² were used to calculate the upper limits of normal heart weight in relation to total body length. It was decided that hearts falling into normal and abnormal weight groups should not be separated sharply, but divided by a "borderline" zone that was arbitrarily established to include all hearts falling within plus and minus 25 Gm. of the upper limit of normal for a given body length. Thus, normal hearts were those weighing less than 25 Gm. below Zeek's upper limit of normal. Abnormally heavy hearts were those heavier than 25 Gm. above that limit.

Abnormally heavy hearts were considered as showing left ventricular hypertrophy. These were divided into 3 groups showing degrees of cardiac hypertrophy: lesser degree of hypertrophy, weighing less than 450 Gm.; moderate hypertrophy, between 450 and 550 Gm.; severe hypertrophy, those above 550 Gm. Some of the abnormal hearts showed hypertrophy of the right as well as the left ventricle. It was considered that a heart in which the ratio of left-to-right ventricular wall thickness was 3 to 1 or less showed an appreciable degree of right ventricular hypertrophy.

Initially, the clinical records had not been examined and only the principal clinical diagnosis was known at the time of the review of the electrocardiograms. However, in cases wherein left ventricular hypertrophy was thought to be absent at necropsy, a careful review of the clinical records was made in order to determine the presence or absence of any clinical evidence of cardiac disease or any possible cause for left ventricular hypertrophy.

RESULTS

The electrocardiographic diagnosis of left ventricular hypertrophy was made in 108 cases; it was confirmed pathologically in 75 cases, was considered questionable in 16 cases, and was not confirmed in 17 cases. In 24 of

the 108 cases the hearts weighed less than the predicted upper limit of normal for body length, but 7 of those fell in the borderline group.

Before these 17 cases were accepted as false-positive cases, a careful review of clinical records was made. In none of them did the past history or final illness suggest a reason for left ventricular hypertrophy. Table 2 summarizes the pertinent clinical information and the essential electrocardiographic findings in the 17 false-positive cases. It is seen that none of the patients died of cardiovascular disease. It was furthermore noted that in no case was cardiac disease or hypertension present during the period of observation, nor was there a history thereof. Pathologic examination revealed the presence of myocardial scarring in 4 patients and myocardial metastasis in 1. The majority of these patients died of non-cardiac malignant tumors and showed emaciation.

A review of the electrocardiographic findings in this group showed that high voltage was present in all but 1 case. In addition, 6 patients showed lesser degree of ST-T abnormalities and 1 showed inversion of T waves in leads V_4 to V_6 . It is noteworthy that of the 7 patients whose electrocardiograms showed ST-T abnormalities, in 4 fibrosis of the myocardium was demonstrated. Six patients showed delayed ventricular activation time in leads V_5 and V_6 .

Thus, 17 patients who had no clinical evidence of cardiac disease and had no more than microscopic or focal myocardial changes at autopsy showed electrocardiographic evidence of left ventricular hypertrophy.

Table 3 summarizes electrocardiographic findings arranged by the 3 groups of criteria in the false-positive cases, in the borderline group, and in cases with pathologically confirmed left ventricular hypertrophy grouped by heart weights. It is seen that high voltage was present in all but 7 cases. It is noteworthy, however, that the false-positive group shows an appreciable number of cases in which high voltage was observed both in extremity and in precordial leads. The incidence of delayed

TABLE 2.—Summary of Findings in the Seventeen Cases of the False-Positive Group

Age	Autopsy diagnosis	Wasting	Heart weight (Gm.)	Criteria for electrocardiographic diagnosis of left ventricular hypertrophy				Remarks
				Incr. voltage	VAT	ST-T	Posit.	
26	Chorionic epithelioma	+	170	$SV_1 + RV_{5,6}$ aV_F	V_5		V	
75	Carcinoma of left lung	+	240	$SV_1 + RV_{5,6}$			V	Minor scarring LV wall
57	Carcinoma of prostate	+	250	$SV_1 + RV_{5,6}$		T flat V_5 & V_6	V	Microsc. fibrosis L V
80	Carcinoma of bladder	+	265	$SV_1 + RV_{5,6}$		S-T depr. T inv. V_4 , V_5 , V_6	I	Anter. wall focal fibrosis
83	Carcinoma of parotid gland	+	260	$R_1 + S_3$ R_{aVL}		T flat $V_{5,6}$	H	Left axis deviation
47	Glioblastoma	+	275	$R_1 + S_3$ R_{aVL}	V_5 V_5		V	
61	Carcinoma of lung	+	305	$SV_1 + RV_{5,6}$	V_5, V_6		I	
60	Carcinoma of prostate	0	290	$SV_1 + RV_{5,6}$		T flat $V_{5,6}$	I	
74	Adenocarcinoma of gallbladder	+	300	$R_1 + S_3$ $SV_1 + RV_{5,6}$		T flat $V_{5,6}$?	
25	Sarcoma of thigh	+	325	R_{aVL} $SV_1 + RV_{5,6}$	V_5	T flat $V_{5,6}$	H	
51	Endothelioma	0	320		$V_{5,6}$		SV	
60	Cirrhosis of liver	0	320	R_{aVL} $SV_1 + RV_{5,6}$			H	Left axis deviation
35	Astrocytoma	+	340	$SV_1 + RV_{5,6}$ R_{aVF}			V	
63	Lymphosarcoma	+	330	$SV_1 + RV_{5,6}$			V	Some myocard. scarring
34	Melanoma	+	320	$SV_1 + RV_{5,6}$	V_5	T flat in $V_{5,6}$	SV	Myocardial metastasis
38	Subarachnoid hemorrhage	0	320	$SV_1 + RV_{5,6}$			V	
60	Carcinoma of pancreas	+	300	$SV_1 + RV_{5,6}$ R_{aVL}			H	

VAT, prolonged ventricular activation time; ST-T, abnormalities of the ST-T portion of the electrocardiogram; V, vertical; SV, semivertical; I, intermediate; H, horizontal.

ventricular activation time in left precordial leads does not show a significantly different incidence between the negative and the positive groups. Abnormalities of the ST-T part of the ventricular complexes occur in positive and negative cases alike. Lesser degrees of such changes (ST depression and flattened T waves) show no major difference in incidence between the various groups. However, inverted T waves appear to occur almost exclusively in the positive cases. It is noteworthy, however, considering the fact that T-wave abnormalities are thought to be late effects of left ventricular hypertrophy, that not all of the heaviest hearts show T-wave changes and that 6 of the 40 cases in the heaviest group, which is 15 per cent, show essentially normal ST-T positions of the electrocardiogram.

Table 4 was constructed in order to examine a possible relationship between left ventricular hypertrophy and the position of the mean electric axis in the frontal plane. It shows the incidence of tracings showing the electric positions according to the conventional classification of Wilson in the negative group, the borderline group, the 3 positive groups, and in cases where the ratio of left-to-right ventricular-wall thickness suggested combined ventricular hypertrophy. There appears to be only a slight preponderance of a more horizontal rotation in heavier hearts than in lighter and in false-positive cases. The distribution of cases in the last column suggests that combined ventricular hypertrophy¹³⁻¹⁵ may have some effect of rotating the mean axis into a more vertical position, but this cannot be demonstrated in a significant manner in this small series.

Table 5 shows the incidence of single electrocardiographic criteria compared with combined criteria. It is noted that electrocardiograms showing more than 1 criteria appear to be more reliable in the diagnosis of left ventricular hypertrophy. A combination of high voltage or increased ventricular activation time with inversion of T wave appears to be the most specific combination for the diagnosis.

DISCUSSION

The interpretation of the findings of this study has been approached with a great deal of caution because of the difficulty in the pathologic definition of what constitutes left ventricular hypertrophy. The most satisfactory method of determining the presence of left ventricular hypertrophy is the direct determination of left ventricular weight after the separation of the musculature of the 2 ventricles, as suggested by Lewis and others.^{16, 17} The time-consuming preparation of such a specimen, however, does not permit routine use of this method for necropsies outside a selected and limited study. Investigation based on routine autopsy material can take into account either the measurement of the thickness of left ventricular wall or the total heart weight. Measurement of left ventricular wall is the less reliable of the 2 indices because of the variability of thickness in various parts of the heart, making comparison difficult, and because of unreliability of such a measurement in the presence of cardiac dilatation. On the other hand, left ventricular musculature accounts for at least 75 per cent of the total cardiac weight, so that its hypertrophy will bring the total cardiac weight promptly out of the normal range, whereas right ventricular hypertrophy would affect total weight only in severe cases. In this study, in particular, the unlikely possibility of isolated right ventricular hypertrophy being responsible for increased total heart weight is almost entirely eliminated by the selection of the material, for only cases with electrocardiographic evidence of left ventricular hypertrophy were included. It was considered, therefore, that the most suitable index for left ventricular hypertrophy for this study was the increase in total cardiac weight, with the use of predicted weight values related to body length. The elimination of the borderline cases served as a better way to separate the normal and abnormal. On the other hand, the diagnosis of right ventricular hypertrophy had to depend on the much less reliable measurement of its wall thickness. An

TABLE 3.—*The Distribution of Electrocardiographic Criteria in the Various Groups According to Heart Weights*

	Negative group	Borderline group	Positive group		
			Hearts less than 450 Gm.	Hearts 450-550 Gm.	Hearts over 550 Gm.
No. of cases	17	16	10	25	40
Criteria:					
High precordial voltage	14	12	7	23	37
High extremity voltage	8	4	3	5	8
High voltage, both planes	6	2	1	4	7
Total high voltage	16	14	9	24	38
Prolonged ventricular activation time	6	7	5	13	22
Depressed					
S-T segments and/or flattened T waves	6	4	4	10	5
Inverted					
T waves	1	5	5	12	29
Total ST-T changes	7	9	9	22	34

arbitrary ratio of thickness of the 2 ventricular walls of 3 to 1 or less, was accepted as evidence that right ventricular hypertrophy is present in addition to left ventricular hypertrophy.

The decision to use total cardiac weight as a pathologic index of normality and to eliminate borderline cases was fully rewarded by the finding that in none of the 17 cases considered normal by such criteria was there clinical evidence of any factor that might have led to left ventricular hypertrophy. Thus, with no clinical evidence of left ventricular overload and no pathologic evidence of hypertrophy, this group of 17 cases could be unequivocally accepted as showing false-positive electrocardiographic findings for an acceptable diagnosis of left ventricular hypertrophy.

This group constitutes 16 per cent of cases in which the generally accepted electrocardiographic criteria for the diagnosis of left ventricular hypertrophy have been applied. The failure of such criteria in these 17 cases constitutes the most important finding of this study. The principal question appears to be what is the reason for an apparently normal heart producing an abnormal electrocardiographic tracing?

In answering this question, it should be pointed out that electrocardiographic criteria for the diagnosis of left ventricular hypertrophy are empirical, but have some theoretical basis. In the first place, the increased muscle mass creates a higher electric potential in the process of depolarization, thus accounting for the increased voltage. Furthermore, a longer time is required to depolarize the thickened muscle, which may be shown in the electrocardiogram by the delay in the onset of the intrinsic deflection and the prolongation of the QRS complexes, particularly the R wave in left-sided precordial leads. Finally, the repolarization process is altered either by the increased muscle mass or by the increased tension of the overloaded muscle resulting in ST-T changes in the electrocardiogram.

The finding, that in an appreciable number of cases abnormally high voltage is recorded in the electrocardiogram in the absence of increased left ventricular mass could be explained in 2 ways: either the normal heart can, under some circumstances, generate stronger depolarization forces, or some electrocardiographic leads may exaggerate and magnify a normal depolarization force. The first possibility is unlikely. On the other

TABLE 4.—*Electric Positions in the Various Groups According to Autopsy Findings*

Position	Total	Negative group	Borderline group	Positive group			
				Hearts less than 450 gm.	Hearts 450 to 550 gm.	Hearts over 550 gm.	LV:RV 3:1 or less
Horizontal	27	4	4	5	6	8	1
Semi-horizontal	21	—	1	2	9	9	4
Intermediate	26	4	3	1	9	9	4
Semi-vertical	15	2	5	—	—	8	—
Vertical	18	7	2	2	1	6	2

hand, exaggeration of the electric potential by various indirect leads is a well-known phenomenon. Conventional extremity leads reflect fairly accurately a projection of the spatial mean vector, representing the main electric forces, onto the frontal plane. Precordial leads reflect the electric forces projected onto the transverse plane. Under ideal circumstances, the magnitude of the spatial mean vector could be accurately ascertained from its projection onto 2 planes. However, this relationship is marred in the human body by the variability of the conductivity of the transmitting media and by the unequal distances of the electrodes from the heart. It is generally agreed that extremity leads reflect electric forces more accurately than do precordial leads. The nearness of the precordial electrode to the heart distorts the electrocardiogram by magnifying the voltage of complexes. In children, adolescents, and young adults unusually high voltage is common in precordial leads. This is thought to be due to the thin chest and close proximity of the electrodes to the heart. Findings of this study demonstrate that a similar distortion may occur in older individuals. Most of the false-positive cases occurred in patients with considerable body emaciation caused by malignant tumors. This offers a reasonable explanation in some, though not all, cases. Other possibilities causing undue magnification of precordial QRS voltage could include vagaries of the anatomic position of the heart in the thorax, or changes in conductivity of the media between the heart and the electrode.

Prolonged ventricular activation time, meas-

ured in left-sided precordial leads, was the next most common criterion of left ventricular hypertrophy found in the false-positive group, having been abnormal in 6 of the 17 cases. It is noteworthy that it appears to be an unreliable diagnostic sign as evidenced by the fact that in almost half of the cases with the heaviest hearts, the ventricular activation time was normal. Inasmuch as there is no reason to doubt the validity of the relationship between the thickness of the muscle mass and the duration of the ventricular activation time in the direct electrogram, one has to conclude that the conventional precordial electrocardiogram may exaggerate or minimize its duration. Whether this is caused by the distance between the electrode and the heart or by a more tangential spread of the depolarization process¹⁸ is unknown.

Abnormalities of the ST-T portion of the electrocardiogram associated with left ventricular hypertrophy are the subject of controversy. The point in question is whether the alteration of the repolarization process that rotates the main ST and T forces away from the main QRS forces is caused by the increase in the muscular mass, thus being another direct effect of left ventricular hypertrophy, or is caused by changes developing secondarily to the hypertrophy or to the disease process, such as increased tension, relative ischemia, etc. This second viewpoint has been responsible for the use of the term "ventricular strain"^{6,8} to connote ST-T changes as opposed to "ventricular hypertrophy," which is applied to increased QRS voltage¹⁹ and increased ventricular activation time. This study

TABLE 5.—*Summary of Electrocardiographic Criteria in Positive and in Negative Cases*

	Negative cases	Positive cases
High voltage alone	6	5
High voltage and increased activation time	4	4
High voltage, depressed S-T segments and flat T waves	5	10
High voltage and inverted T waves	1	14
Increased ventricular activation time and inverted T waves	—	3
High voltage, increased ventricular activation time and lesser ST-T changes	1	11
High voltage, increased ventricular activation time and inverted T waves	—	28

cannot shed light on this controversy. It does demonstrate, however, the importance of adding the ST-T abnormalities to the criteria of left ventricular hypertrophy, which otherwise, if it were to be based on increased voltage and delayed activation time, could never be diagnosed with certainty. To be sure, S-T segment depression, flattening and inversion of T waves are electrocardiographic abnormalities that can be caused by a great variety of pathologic and physiologic processes. Yet such abnormalities, when combined with increased voltage and prolonged activation time, add to the specificity of diagnostic criteria of left ventricular hypertrophy. The more advanced change, the inversion of T waves in leads with strongly positive QRS complexes, appears the most valuable addition to the diagnostic criteria, for only once was such change found in the false-positive group, and that was in a case in which focal fibrosis of the myocardium was present, which was the obvious cause of this electrocardiographic abnormality. Lesser ST-T abnormalities, such as S-T segment depression and flattening of T waves were found occasionally in the false-

positive cases. Some such cases, though not all, showed the presence of focal disease of the myocardium. It is also possible that such electrocardiographic abnormalities might have been caused by the tendency of the T-wave vector to rotate more vertically and anteriorly in elderly individuals,²⁰ whereby flat T waves appear in left precordial leads.

Abnormalities of the repolarization process appear to be such an integral part of the electrocardiographic pattern of left ventricular hypertrophy that it was thought to be preferable to use the all-inclusive term "hypertrophy" rather than the dual concept of "hypertrophy" and "strain." The concept of strain appears to have some merit in acute processes wherein S-T and T changes appear or disappear under circumstances in which the time is too short for the development or the regression of ventricular hypertrophy. However, until more is known about the exact nature of "strain," it may be assumed that it represents the same physiopathologic process that stimulates the growth of heart muscle.

The findings of this study suggest strongly that presently available criteria for the electrocardiographic diagnosis of left ventricular hypertrophy are reasonably satisfactory. Yet, on the one hand, normal hearts can undergo depolarization and repolarization in such a manner that conventional electrocardiographic tracing shows a seemingly abnormal picture, and, on the other hand, grossly hypertrophied hearts can, under some circumstances, present a near-normal electrocardiogram. This is presumably caused by the various distortions of the electric activity of the heart in their projections onto the conventional electrocardiographic leads. Because of these distortions, the magnitude, the direction, and the duration of the electric forces cannot be estimated accurately, so that no absolute criteria separating normal tracings from those of left ventricular hypertrophy can exist. Rather, one should consider electrocardiographic criteria for the diagnosis of left ventricular hypertrophy as expressing a probability that the left ventricle

is hypertrophied. Such probability appears to be higher in the presence of an average body build, and lower in the presence of emaciation, thin chest wall, or some other factor capable of distorting the transmission of the electric cardiac potential.

The greatest possibility of error in the diagnosis of left ventricular hypertrophy lies in the diagnosis of early hypertrophy. The characteristic picture of fully developed left ventricular hypertrophy consisting of leftwards (horizontal) rotation of the mean QRS axis, the high voltage, the delayed ventricular activation time, the prolonged QRS duration, and the characteristic S-T segment deviation and T-wave inversion are very unlikely to lead to a diagnostic error. However, it is important to note that severe hypertrophy of the left ventricle may exist while fulfilling only one of these criteria, so that the electrocardiographic diagnosis of "early" and "late" or "mild" and "severe" hypertrophy may be subject to a considerable error.

Throughout the study, an attempt has been made to visualize alterations of the electrocardiogram as a variation of the sequence of activation and the magnitude of the spatial electric forces, rather than as changes in the contour of the various waves. One is justified in asking the question, whether direct vectorecardiography would be superior in the diagnosis of left ventricular hypertrophy to conventional electrocardiography. At the present time, no uniform standards exist and the information at hand is yet inconclusive. However, it is doubtful that this method will succeed in the area in which conventional electrocardiography is most disappointing: the separation of early left ventricular hypertrophy from the normal heart.

SUMMARY

In a series of 550 unselected electrocardiograms taken on patients in whom necropsy findings were later available, 108 tracings showed the pattern of left ventricular hypertrophy according to currently accepted electrocardiographic criteria. The analysis of the necropsy findings based on heart weights re-

vealed that left ventricular hypertrophy was believed to be present in 75 cases, absent in 17 cases, and questionable in 16 cases.

A careful analysis of the 17 cases with normal cardiac weights was made and it was found that in none of the cases was there known cause for cardiac hypertrophy, nor was there significant cardiac disease present. The majority of patients in this group died of malignant disease and showed considerable emaciation.

The value of the 3 principal classes of electrocardiographic criteria was examined not only in the light of confirmed and false-positive cases, but also according to their incidence in cases with mild, moderate, and severe left ventricular hypertrophy determined by cardiac weight. The prolonged ventricular activation time was found to be the least reliable sign, having been present in many false-positive cases and absent in some cases with severe hypertrophy. Increased voltage of precordial leads, the most sensitive of the criteria, was present in most cases. It was also, however, most frequently responsible for a false-positive diagnosis of left ventricular hypertrophy. The depression of S-T segments, flattening and inversion of T waves in leads showing the highest electro-positive deflections when added to the other 2 groups of criteria materially increased the specificity of the diagnosis. However, the relationship between the extent of the electrocardiographic abnormalities and the severity of hypertrophy is only fair.

It is believed that these inaccuracies in the electrocardiographic diagnosis are inherent in the method and demonstrate the fact that conventional electrocardiography registers in a rather crude way the electric forces of cardiac action, being influenced in addition by such extraneous factors as body build, vagaries of anatomic positions of the heart, the degree of insulating effect of outside structures, and probably other, as yet unknown, factors.

Presently available electrocardiographic criteria for the diagnosis of left ventricular hypertrophy appear to be moderately satis-

factory. They have to be applied, however, with the understanding of their limitations: it is necessary to accept them as an expression of probability rather than a diagnosis of left ventricular hypertrophy. The disappointing inaccuracy of electrocardiography in the field of the diagnosis of early left ventricular hypertrophy is emphasized.

ACKNOWLEDGMENT

The authors are indebted to Dr. John B. Frerichs, Chief of Pathological Anatomy, Veterans Administration Hospital, and to the members of his Department for making the autopsy material available for this study.

SUMMARY IN INTERLINGUA

In un serie de 550 non-seligite electrocardiogrammas, obtenite ab patientes pro qui reportos necroptie deveniva subsequentemente disponibile, 108 exhibiva le configuration de hypertrophia sinistro-ventricular secundo le currentemente acceptate criterios electrocardiographic. Le analyse del reportos necroptie revelava pesos cardiac indicante le presentia de hypertrophia sinistro-ventricular in 75 casos e su absentia in 17 casos. In 16 casos le reporto necroptie esseva indecise.

Un analyse meticulose del 17 casos con normal pesos cardiac esseva effectuate. Esseva constatate que il existeva in nulle de iste casos un causa cognoscite de hypertrophia cardiac, e nulle esseva characterisate per le presentia de significative lesiones cardiac. Le majoritate del patientes in iste gruppo moriva ab morbos maligne e exhibiva grados considerabile de emaciation.

Le valor del 3 classes principal de criterios electrocardiographic esseva examinate non solamente in le lumine de casos confirmate e de casos false-positive sed etiam con referentia a lor incidentia de casos de leve, moderate, e sever hypertrophia sinistro-ventricular, judicate super le base del pesos cardiac. Esseva trovate que prolongation del tempore de activation ventricular es le minus fidel del signos de hypertrophia sinistro-ventricular. Illo esseva presente in numerose casos false-positive e absente in plures con hypertrophia sever. Augmento de voltage in de-

rivationes precordial esseva le plus sensibile del criterios. Su presentia esseva notate in le majoritate del casos, sed illo esseva etiam responsabile pro un plus grande portion del diagnoses false-positive que non importa qual altere criterio de hypertrophia sinistro-ventricular. Le depression del segmento S-T e le applanation e inversion del unda T in derivationes exhibiente le plus alte deflexiones electro-positive—addite al criterios del 2 altere gruppos—augmentava le specificitate del diagnose a grados significative. Tamen, le relation inter le extension del anormalitates electrocardiographic e le grado de severitate del hypertrophia es solamente "satis bon."

Es formulate le opinion que iste inexactitudes del diagnose electrocardiographic inherere in le methodo mesme e servi a demonstrar le facto que le electrocardiographia conventional registra le fortias del action cardiac in un maniera pauco raffinate, proque illo es influentiate etiam per varie factores extranee, como per exemplo le conformation del corpore del patiente, le erratic variationes in le position anatomic del corde, le grado del effecto isolatori de structuras externe, etc., incluse, il es probabile, un numero de factores que es ancora incognoscite.

Le currentemente disponibile criterios electrocardiographic pro le diagnose de hypertrophia sinistro-ventricular pare esser "moderatemente satisfactori." Tamen, illos debe esser applicate in plen recognition de lor limitationes. Il es necessari acceptar los como expression de probabilitate plus tosto que como diagnostic pro hypertrophia sinistro-ventricular. Es sublineate le disappuntante inexactitude del electrocardiographia in le campo del diagnose de hypertrophia sinistro-ventricular in stadios precoce.

REFERENCES

1. GUBNER, R., AND UNGERLEIDER, H. E.: Electrocardiographic criteria of left ventricular hypertrophy. *Arch. Int. Med.* 72: 196, 1943.
2. WILSON, F. N., JOHNSTON, F. D., ROSENBAUM, F. F., ERLANGER, H., KOSSMAN, C. E., HECHT, H. H., COTRIM, N., DEOLIVEIRA, R., AND

- BARKER, P. S.: The precordial electrocardiogram. *Am. Heart J.* 27: 19, 1944.
3. KATZ, L. N.: Electrocardiography. Ed. 2. Philadelphia, Lea and Febiger, 1946.
 4. NOTH, P. H., MYERS, G. B., AND KLEIN, H. A.: Precordial electrocardiogram in left ventricular hypertrophy. *J. Lab. & Clin. Med.* 32: 1517, 1947.
 5. GOLDBERGER, E.: Unipolar Lead Electrocardiography. Ed. 2. Philadelphia, Lea and Febiger, 1949.
 6. SOKOLOW, M., AND LYON, T. P.: The ventricular complex in left ventricular hypertrophy as obtained by unipolar precordial and limb leads. *Am. Heart J.* 37: 161, 1949.
 7. SCHACK, J. A., ROSENMAN, R. H., AND KATZ, L. N.: The aV limb leads in the diagnosis of left ventricular strain. *Am. Heart J.* 40: 696, 1950.
 8. GOULDER, N. E., AND KISSANE, R. W.: The contributions of the augmented unipolar extremity leads to the pattern of left ventricular hypertrophy in the horizontal and semi-horizontal electrocardiographic position. *Am. Heart J.* 42: 88, 1951.
 9. DIMOND, E. G.: Electrocardiography. St. Louis, C. V. Mosby Co., 1954, p. 253.
 10. SCOTT, R. C., SEIWERT, V. J., SIMON, D. L., AND MCGUIRE, J.: Left ventricular hypertrophy: A study of accuracy of current electrocardiographic criteria when compared with autopsy findings in one hundred cases. *Circulation* 11: 89, 1955.
 11. SAPHIR, O.: Autopsy Diagnosis and Techni-
 - que. Ed. 2. New York, P. B. Hoeber, Inc., 1946.
 12. ZEEK, P. M.: Heart weight. I. The weight of the normal human heart. *Arch. Path.* 34: 820, 1942.
 13. ROSENMAN, R. H., KRAUSE, D., HWANG, W., AND KATZ, L. N.: The electrocardiographic diagnosis of combined left and right ventricular strain. *Am. Heart J.* 40: 453, 1950.
 14. PAGNONI, A., AND GOODWIN, J. F.: Electrocardiographic diagnosis of combined ventricular hypertrophy. *Brit. Heart J.* 14: 451, 1952.
 15. LIPSETT, M. B., AND ZINN, W. J.: Anatomic and electrocardiographic correlation in combined ventricular hypertrophy. *Am. Heart J.* 45: 86, 1953.
 16. LEWIS, T.: Observation upon ventricular hypertrophy with especial reference to preponderance of one or other chamber. *Heart* 5: 367, 1914.
 17. FULTON, R. M., HITCHINSON, E. O., AND MORGAN JONES, A.: Ventricular weight in cardiac hypertrophy. *Brit. Heart J.* 14: 413, 1952.
 18. DIMOND, E. G.: Electrocardiography. St. Louis, C. V. Mosby Co., 1954, p. 106.
 19. WINSOR, T., AND BECKNER, G.: Hypertrophy of the heart; electrocardiographic distinction between physiologic and pathologic enlargement. *California Med.* 82: 151, 1955.
 20. GRANT, R. P., AND ESTES, E. H.: Spatial Vector Electrocardiography. Philadelphia, Blakiston Co., 1951, p. 57.



Stewart, J. W., and Acheson, E. D.: Atherosclerosis in a Haemophiliac. *Lancet* 1: 1121 (June 1), 1957.

The authors report the clinical and postmortem findings in the case of a 73-year-old man who had suffered a coagulation defect since childhood diagnosed hemophilia on the basis of a prolonged coagulation time and a thromboplastin-generation test indicative of deficient antihemophilic globulin. He had experienced angina pectoris for 3 years before his death, which occurred during an episode of gastrointestinal bleeding. At postmortem examination, atheroma of the coronary arteries and aorta was found. It is suggested that such a case is evidence against Duguid's theory of the thrombotic origin of atheroma.

KURLAND

Dextrocardia with Pulmonary Stenosis and Functionally Single Right Ventricle

By JOSEPH FISHER, M.D., AND SOON KYU SUH, M.D.

An unusual case of congenital heart disease is reported which, despite numerous circulatory abnormalities, permitted a life span of 34 years.

THIS is an unusual case of congenital heart disease in a patient with dextrocardia and situs inversus in which both the aorta and stenosed pulmonary artery originated from the right ventricle. Despite numerous circulatory abnormalities, this patient lived 34 years.

CASE REPORT

A 34-year-old Puerto Rican was admitted to Lincoln Hospital February 10, 1956, complaining of chest pains, vomiting, marked dyspnea, and ankle edema.

According to the mother, the child was normal at birth and developed normally to about the age of 8. Then he began to develop a deformity of his back and to show cyanosis. Dyspnea on exertion, cyanosis, and deformity of the back became progressively worse, but he was not under any continuous medical care.

Examination at the time of admission revealed an acutely ill, markedly dyspneic, and cyanotic man. There was marked deformity of the thoracic cavity due to kyphoscoliosis of the dorsal spine with a convexity to the left. The blood pressure was 100/60. The heart rate was very rapid and irregular. There was a grade IV, rough systolic murmur and a long blowing diastolic murmur at the fourth left interspace, and a grade IV systolic murmur over the second left interspace. Moist rales were heard throughout both lung fields. There was heaving over the entire precordial area and a point of maximum cardiac impulse could not be determined. The thrust to the right of the sternum appeared to be greater than to the left. The liver was enlarged 4 fingers below the left costal margin. There was 3+ pitting edema of the extremities.

Fluoroscopy and x-ray of the heart were confusing because of the kyphoscoliosis. The aorta was to the right of the esophagus and the transverse diameter of the heart was increased. The stomach was in the right upper quadrant (fig. 1).

The electrocardiogram (fig. 2) was most difficult to interpret. Atrial fibrillation with a very rapid ventricular rate and digitalis effect were definite. There was no definite evidence of dextrocardia. The hemoglobin was 15 Gm. per cent and the white

count was 6,400, with a normal differential. The urea nitrogen was 28 mg. per cent. Other tests were within normal limits.

The patient was treated with digitalis, mercurials, quinidine, and a salt-free diet, and the decompensation improved. However, on April 14, he complained of pains in the chest and marked dyspnea, went into shock, and died.

Autopsy Findings

At autopsy, the heart was predominantly in the right chest (fig. 3). The ascending aorta was on the left with the descending portion on the right side of the esophagus. There was marked dilatation and hypertrophy of the right* atrium and right ventricle, which were on the left side of the heart. The left atrium and left ventricle were very small and were posterior and on the right side. In the heart, both the aorta and stenosed pulmonary artery arose from the markedly enlarged right ventricle. The aortic valves appeared normal, except for fenestrations of the cusps. The narrowed opening of the pulmonary artery (which was about 0.5 cm. in diameter) was below and to the right of the aortic opening (fig. 4). The pulmonary valve had only 2 cusps. The pulmonary artery was directed posterior to the aorta, and from right to left. There was an interventricular septal defect measuring about 2 cm. (fig. 5). in diameter in the muscular portion of the septum and below the crista supraventricularis. It did not involve the openings of either the pulmonary artery or aorta. The myocardium appeared normal in color and consistency. One coronary artery arose from the aorta and one from the pulmonary artery. The right pulmonary veins emptied into the right atrium. A patent ductus arteriosus was not found. The liver weighed 1250 Gm. There was situs inversus of all the organs, including the lungs, except the cecum and appendix, which were on the right side.

* To avoid misunderstanding, right atrium and right ventricle refer in this article to the atrium and ventricle supplying the pulmonary circulation although they were on the left side of the heart. The left atrium and left ventricle refer to the systemic circulation and were on the right side.



FIG. 1. Posteroanterior x-ray of chest showing marked deviation of the esophagus to the left in the upper portion. As the esophagus descends, it deviates to the right to empty into the stomach in the right upper quadrant.

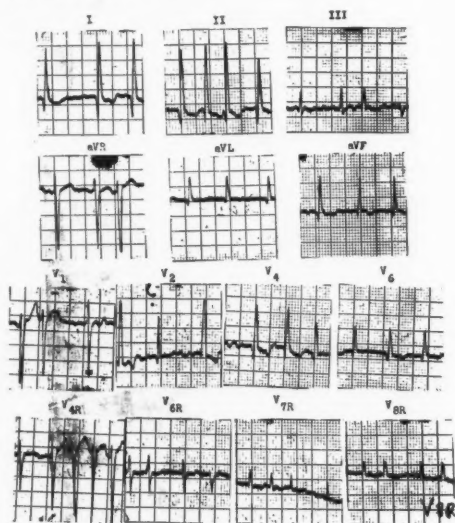


FIG. 2. Electrocardiogram showing atrial fibrillation and digitalis effect.

DISCUSSION

The diagnosis of dextrocardia was clinically difficult to establish for the following reasons. Because of the large right ventricle, the electrocardiogram was not diagnostic of dextrocardia. Since there was atrial fibrillation, the direction of the P waves could not be deter-



FIG. 3. Exterior view of the heart. The entire anterior aspect consists of right atrium and right ventricle.

mined. The marked scoliosis and kyphosis caused marked distortion of the thoracic cavity with rotation of the heart, so that chamber size could not be determined on either fluoroscopy or x-ray examination. Fluoroscopy revealed a right-sided aorta, equal pulsations on both sides of the cardiac shadow in the posteroanterior view, and situs inversus. Physical examination revealed a heaving over the anterior chest, so that a point of maximum cardiac impulse could not be determined. Neither angiocardiology nor cardiac catheterization could be performed.

Although both levocardia in situs inversus¹ and isolated dextrocardia² are nearly always associated with congenital cardiac defects, the occurrence of congenital cardiac defects in dextrocardia with situs inversus is more unusual.³ In Maude Abbott's 1,000 cases, there were 11 cases of dextrocardia, situs inversus, and cardiac defects. The incidence of a patent right ventricular aorta is rare. Edwards⁴ mentioned 8 cases of this abnormality. Also, in Abbott's series,⁵ there were 3 cases of aorta originating from the right ventricle. Neither Edwards' nor Abbott's cases showed dextrocardia with situs inversus.

It is difficult to classify this type of abnormality. Although this patient had the 4 charac-

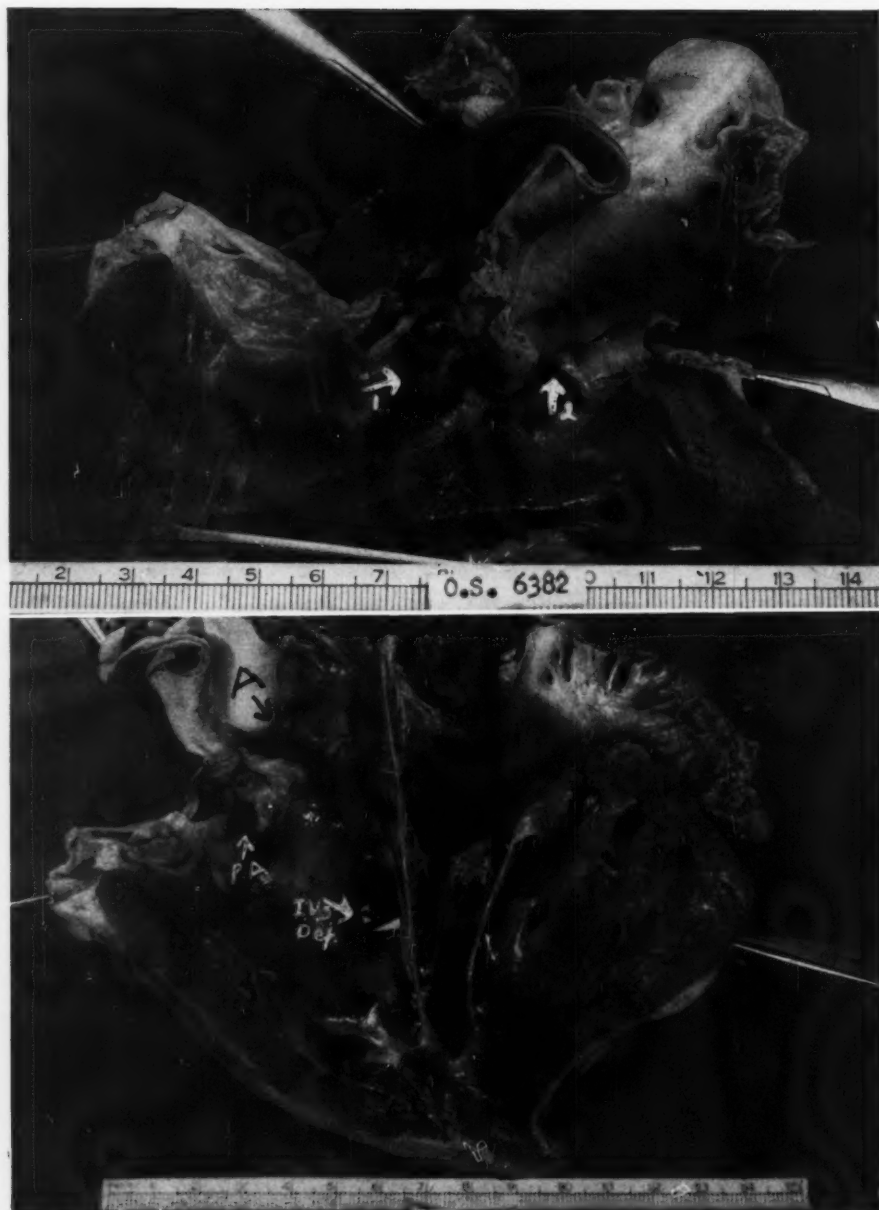


FIG. 4. *Top*. Arrow no. 1 points to stenosed pulmonary artery. Arrow no. 2 points to opening of aorta.

FIG. 5. *Bottom*. Shows tricuspid valve and relationship of interventricular septal defect to openings of aorta and stenosed pulmonary artery. Note that there is no overriding of either the aorta or the pulmonary artery.

teristic defects usually classified as tetralogy of Fallot, namely right-sided aorta, pulmonary stenosis, interventricular septal defect, and right ventricular hypertrophy, there was no overriding of the aorta over the septal defect. Also, there was no overriding of the stenotic pulmonary artery. The ventricular septal defect was below the crista supraventricularis, in the muscular part of the septum, and the course of the pulmonary artery was directed posterior to the aorta from right to left. In Taussig's³ description of the types of tetralogy, there is always some degree of overriding of the aorta. Even if one does not accept this concept of overriding of the aorta, the location of the defect and the relationship of the pulmonary artery and the aorta are not those found in the tetralogy of Fallot. This heart would fit into the type II classification of Spitzer.⁶ According to his theory there is a greater degree of detorsion than that found in his type I classification (in which the tetralogy would be placed). As a result, the ascending aorta is to the right (in this case, to the left, because of the dextrocardia) and anterior to the pulmonary artery. Also, Spitzer maintained that the aorta is a right ventricular aortic conus that has reopened and is connected with the common ascending aorta, the left ventricular aortic conus having been obliterated. As a result, there is no direct outflow ostium from the left ventricle. The only means of exit of blood from the left ventricle is through the septal defect into the right ventricle.

Spitzer also stated that the pulmonic valve usually has only 2 cusps and 1 of the coronary arteries is transposed so that it arises from the pulmonary artery. These abnormalities were also present in this case.

The electrocardiogram was most unusual. In spite of the tremendous right ventricle, characteristic right ventricular complexes (R or Rs) were not seen on either the right or left side of the heart. Only in V_1 , V_{4R} , and V_{6R} were RS complexes seen. The unipolar limb leads did not definitely indicate dextroposition. As mentioned previously, because of the atrial fibrillation, the direction of the P waves was of no assistance. In retrospect, one can surmise right ventricular hypertrophy in the dextrocardia

because of the late intrinsicoid deflection of the R wave on the left side of the heart (V_{2-6}) and aV_L with progressive formation of an rS complex as one reads from V_1 to V_{6R} (from right sternal border to right axilla) and the formation of an R complex in V_{7R} and V_{8R} , suggesting a left ventricular complex in the right posterior chest.

It is obvious that there must have been some fairly competent pulmonary collateral circulation to allow this man to live 34 years. No patent ductus arteriosus was found. Ghoreyeb and Karsner⁷ as early as 1913 showed that when the pressure in the pulmonary radicles is markedly reduced the bronchial circulation is brought into service to compensate for the decreased pulmonary flow. The earlier in life that this occurs, the more readily the bronchial arteries enlarge. This pattern of collateral circulation certainly must have occurred in this case, aided undoubtedly by the anterior and posterior mediastinal and esophageal arteries.⁸ It is only through development of these collateral vessels that sufficient pulmonary circulation could be maintained, as the markedly stenosed pulmonary valve certainly could not permit sufficient blood to get to the lungs.

SUMMARY

An unusual case is presented of a 34-year-old man with dextrocardia and situs inversus in which the aorta and stenosed pulmonary artery arose from a markedly hypertrophied and dilated right ventricle. There were numerous other congenital abnormalities, namely, interventricular septal defect, 1 coronary artery arising from the pulmonary artery, bicuspid pulmonary valve, the right pulmonary vein emptying into the right atrium, and fenestration of the cusps of the aortic valve. This combination of congenital cardiac defects best fits in with Spitzer's type II classification of congenital malformations of the heart. There must have been a well-developed collateral pulmonary circulation to allow this man to live 34 years.

SUMMARIO IN INTERLINGUA

Es presentate le caso inusual de un homine de 34 annos de etate, con dextrocardia e sito inverse in que tanto le aorta como etiam le stenotic arteria pulmonar partiva ab un marca-

temente hypertrophic e dilatate ventriculo dextere. Le caso se distingueva per numerose altere anormalitates congenite, i.e. defecto de septo interventricular, 1 arteria coronari a origine in le arteria pulmonar, bicuspidate valvula pulmonar, drainage del vena dextero-pulmonar a in le atrio dextere, e fenestration del cuspides del valvula aortic. Iste combination de congenite defectos cardiac se accorda le melio con le typo II del classification de congenite malformations del corde secundo Spitzer. Viste que iste homine viveva 34 annos, il es necessari supponer que ille haveva un ben-disveloppate circulation pulmonar collateral.

REFERENCES

- ¹ CAMPBELL, M., AND FORGAS, P.: Laevocardia with transposition of abdominal viscera. *Brit. Heart J.* **15**: 401, 1953.
- ² LICHTMAN, S. S.: Isolated congenital dextrocardia. *Arch. Int. Med.* **48**: 683 and 866, 1931.
- ³ TAUSSIG, H. B.: *Congenital Malformations of the Heart*. New York, The Commonwealth Fund, 1947.
- ⁴ EDWARDS, J. E.: Congenital malformations of the heart. In *Pathology of Heart*, Gould, S. E., Ed. Springfield, Ill., Charles C Thomas, 1953, p. 351.
- ⁵ BAUER, D. DE F., AND ASTBURY, E. C.: Congenital cardiac disease: Bibliography of the 1,000 cases analyzed in Maude Abbott's atlas. *Am. Heart J.* **27**: 688, 1944.
- ⁶ SPITZER, A.: Architecture of normal and malformed hearts. *Virchows Arch. path. Anat.* **27**: 226, 1929. Translation by Lev and Vass, Springfield, Ill., Charles C Thomas, 1951. p. 87.
- ⁷ GHOREYEB, A. A., AND KARNER, H. T.: A study of the relationship of pulmonary and bronchial circulation. *J. Exper. Med.* **18**: 500, 1913.
- ⁸ HARRISON, W. F.: Collateral pulmonary circulation in congenital heart disease. *Am. Heart J.* **5**: 213, 1928.

Reagan, L. B., Young, K. R., and Nicholson, J. W.: Ventricular Defibrillation in a Patient with Probable Acute Coronary Occlusion. *Surgery* **39: 482 (Mar.), 1956.**

The authors reported a case of ventricular fibrillation in a patient with acute coronary occlusion, followed by successful restoration of circulation. The patient was a 55-year-old white man who had a typical history of myocardial infarction. At the time that ventricular fibrillation was recorded electrocardiographically the patient lost consciousness. The left side of the chest was immediately opened and massage was started through the intact pericardium. Epinephrine was injected into the left ventricle and an electric defibrillator was utilized. The latter converted fibrillation to asystole, at which time cardiac massage was started. Effective cardiac contractions appeared and the blood pressure rose. Recovery from the operation was uneventful except for slight fever.

ABRAMSON

Anatomic Studies of the Cardiac Conduction System in Congenital Malformations of the Heart

By KEITH REEMTSMA, M.D., AND W. M. COPENHAVER, PH.D.

A frequent and serious complication of certain intracardiac procedures is heart block, produced by operative injury to the conduction pathways. The anatomic relationship of the conduction system to cardiac defects has previously been studied only in isolated cases of heart block. This report deals with a study, by means of serial sections and reconstructions, of the relationships of the atrioventricular node and bundle to a variety of congenital defects in the area of the membranous ventricular septum.

STUDIES on the conduction mechanism of the heart began in 1845 with the observations of Purkinje,¹ who described in sheep hearts a peculiar type of muscle fiber that now bears his name. In 1893 His² published a description of the atrioventricular bundle, and since that time a considerable body of information has accumulated on the structure and function of this specialized tissue. However, except for isolated studies in cases of congenital heart block, there is scant information on the course of the conduction fibers in congenital malformations of the heart.

The development of intracardiac surgery has aroused renewed interest in the anatomy of congenitally malformed hearts, and repair of certain cardiac defects has demonstrated the susceptibility of the conduction system to injury. In an early series of 20 cases of interventricular septal defect repaired by intracardiac operations, 9 instances of conduction disturbances were recorded.³ Recently Cooley, Kirklin, and Harshbarger⁴ stated "knowledge of the exact anatomic location of the bundle of His in the presence of persistent common atrioventricular canal has long been needed, for an inadvertently placed stitch through or around the bundle may lead to complete heart block with fatal termination."⁴

This present report deals with a study of the anatomic relationship of the cardiac conduction system to various congenital defects in the

region of the membranous portion of the interventricular septum and adjacent structures.

MATERIALS AND METHODS

In the initial stages of the investigation, dissection of the conduction system was attempted in fresh and formalin-fixed human hearts after the method described by Widran and Lev.⁵ Microdissection techniques were applied in fresh fetal and neonatal hearts. Neither of these methods, however, appeared satisfactory in the presence of intracardiac defects. The method of study finally adopted involved histologic study and visual reconstruction of serial sections. Five hearts, obtained from the Department of Pathology of Babies Hospital, were selected for study. Table 1 summarizes the malformations present in each case.

Following the photographing and sketching of specimens, a block of tissue was removed that included the ostium of the coronary sinus, the inferior portions of the atrial walls and interatrial septum, the superior portions of the ventricular walls and interventricular septum, and the attached fibrous ring of the heart. This block of tissue completely encircled the defects in the region of the membranous portion of the interventricular septum and the atrioventricular septum. The block was then sectioned in a direction corresponding approximately to the anteroposterior plane of the body. The sections were stained with either hematoxylin and eosin or Masson's triple stain. Following histologic study, graphic reconstructions were made from projected sketches of the slides.

OBSERVATIONS

Case 1. This heart showed a defect in the membranous portion of the interventricular septum. The atrioventricular node was identified on the superior (atrial) aspect of the fibrous ring of the heart, adjacent to the ostium of the coronary sinus. The atrioventricular bundle coursed to the left and caudad, penetrating the fibrous ring. The bundle then followed the posteroinferior aspect of the

From the Departments of Surgery and Anatomy, Columbia University College of Physicians and Surgeons, New York, N. Y.

Supported in part by grant H-3252 from the National Heart Institute, United States Public Health Service.

TABLE 1.—Summary of Atrial and Ventricular Defects in Five Cases

Case no.	Age	Defects
1	2 months	interventricular septal defect (membranous)
2	6 days	persistent atrioventricular canal, patent foramen ovale
3	4 months	interatrial septal defect (primum type)
4	5 weeks	interventricular septal defect (muscular)
5	5 weeks	complete transposition without interventricular septal defect, patent foramen ovale

septal defect, lying immediately beneath the endocardium. The right bundle branch could be identified coursing subendocardially down the ventricular septum; the left bundle branch was indistinct (fig. 1, case 1, and fig. 2).

Case 2. This heart demonstrated a persistent atrioventricular canal and a patent foramen ovale. The atrioventricular node lay on the atrial aspect of the fibrous ring, and the atrioventricular bundle penetrated this fibrous ring in a course similar to that described in case 1. The bundle passed around the posteroinferior aspect of the ventricular portion of the atrioventricular defect. As described in case 1, the bundle lay directly beneath the endocardium. At the lowermost portion of the ventricular defect the bundle divided into right and left bundle branches, which then coursed down the ventricular septum (fig. 1, case 2, and fig. 3).

Case 3. This specimen showed a large interatrial septal defect, only a thin rim of rudimentary atrial muscle remaining on the superior aspect of the fibrous ring. The atrioventricular node and bundle lay in the normal position. However, before penetrating the fibrous ring, the node and bundle were separated from the atrial cavity only by endocardium and a narrow rim of atrial muscle (fig. 1, case 3).

Case 4. In this specimen, the interventricular septal defect was high in position; however it lay

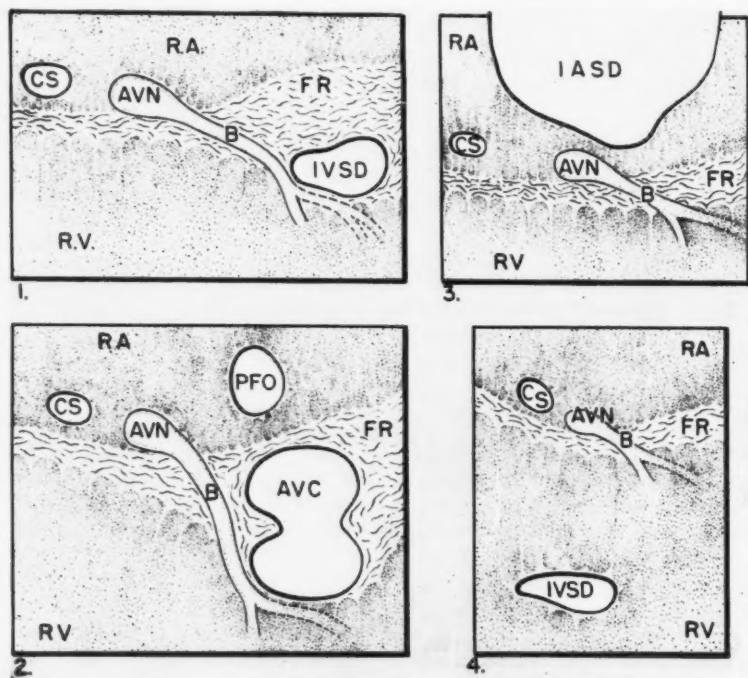


FIG. 1. Reconstructions demonstrating relationships of the atrioventricular node and bundle in cases of (1) interventricular septal defect, membranous portion; (2) atrioventricular canal; (3) interatrial septal defect, primum type; and (4) interventricular septal defect, muscular portion. AVN and B—atrioventricular node and bundle; AVC—atrioventricular canal; CS—ostium of coronary sinus; FR—fibrous ring of the heart; IASD—interatrial septal defect; RA—right atrium; RV—right ventricle.

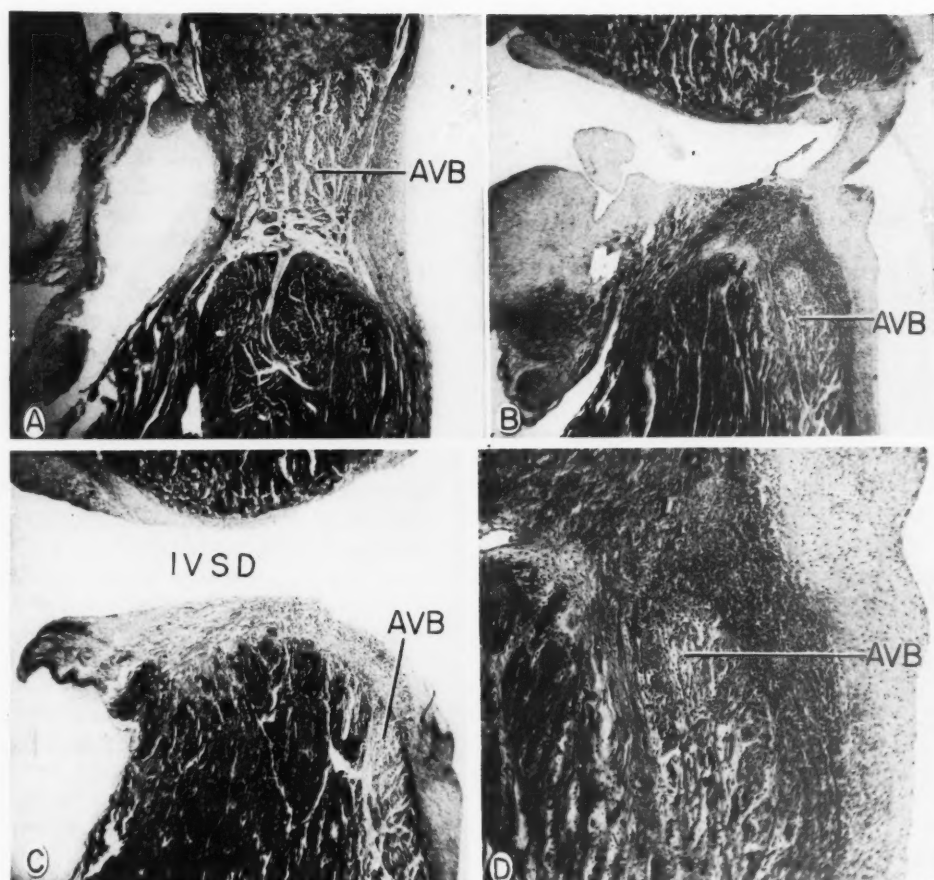


FIG. 2. Photomicrographs of case 1 demonstrating (A) the location of the atrioventricular bundle in the fibrous ring of the heart, above the ventricular muscle; (B) the bundle lying between ventricular muscle and endocardium, with the membranous septum intact; (C) the bundle in a position similar to (B), beneath the interventricular septal defect. A higher magnification (D) shows conductive tissue between ventricular muscle and endocardium. AVB—atrioventricular bundle; IVSD—interventricular septal defect. Masson's triple stain; $\times 30$ A, B, and C; $\times 100$ D.

in the muscular septum posterior to the septum membranaceum. The atrioventricular node and bundle lay in the usual position, close to the membranous septum, which was intact in this case. Distal to the bifurcation of the bundle, the right branch was indistinct (fig. 1, case 4).

Case 5. This specimen showed complete transposition of the great vessels, patent foramen ovale, and an intact interventricular septum. In this case the location of the atrioventricular node and the course of the bundle were normal.

DISCUSSION

During the past 3 decades several reports have appeared on the histologic study of the

conduction system in cases of congenital heart block, associated with intracardiac defects.

In 1925 Wilson and Grant⁶ reported a case of partial heart block in an infant who was found to have a large interventricular septal defect. By studying serial sections of the posterior wall of the heart they observed a well-developed atrioventricular node in the usual location; however they could find no definite bundle penetrating the fibrous ring, although several strands of nodal tissue were seen coursing toward the posterior wall of the ventricle.

In 1929 Yater⁷ reported the first histologic

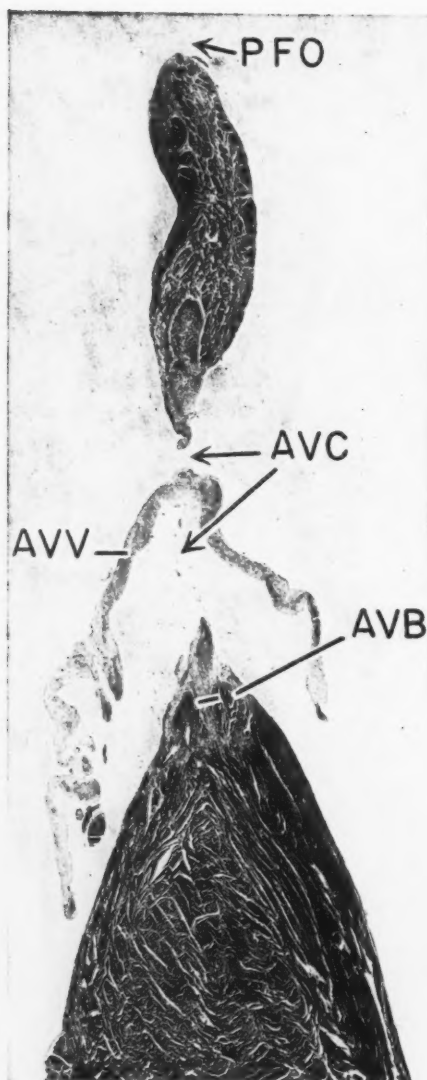


FIG. 3. Low-power photomicrograph of case 2, showing the patent foramen ovale and the atrioventricular canal. The atrioventricular bundle branches lie in the superior portion of the ventricular septum, immediately beneath the ventricular portion of the defect. AVB—atrioventricular bundle; AVC—atrioventricular canal; AVV—common atrioventricular valve; PFO—patent foramen ovale. H and E stain; $\times 15$.

study of the conduction system in a case of complete congenital heart block. This patient demonstrated transposition of the great vessels without septal defect, and serial sections demonstrated that the atrioventricular node was completely separated from the bundle of His by the central fibrous body. In 1933 and 1934, Yater and co-workers^{8, 9} studied an additional 2 cases of complete congenital heart block, both of which were found to have defects in the membranous portion of the interventricular septum. In both cases the atrioventricular node was identified; in one case the bundle of His was separated from the node, and in the other case the bundle of His could not be identified. Similar studies on cases of heart block have appeared sporadically,¹⁰⁻¹² and this material has been summarized in a review of congenital heart block by Donoso, Braunwald, Jick, and Grishman.¹³

Although the location of the atrioventricular bundle in human beings has received little attention in the past, it is a subject of current interest in several laboratories. While our studies were in progress, we learned of research being done by Truex and Kain¹⁴ on conduction tissue in human hearts with high interventricular septal defects. From their demonstration at the American Association of Anatomists in 1956 it appears that their results are comparable to ours in case 1.

In the cases included in this report, hearts with a variety of defects in the region of the membranous portion of the interventricular septum were selected. In the case of the simple defect of the septum membranaceum, the conduction bundle was readily identified coursing along the postero-inferior rim of the defect. A comparable anatomic relationship was observed in the case of atrioventricular canal, with the bundle lying along the postero-inferior rim of the ventricular portion of the defect. Both these defects are believed to be related to a failure of fusion of the dorsal endocardial cushion and the ascending ventricular septum. Walls¹⁵ has observed the atrioventricular bundle in an 8-mm. embryo, and he describes its course as "growing forward under the dorsal endocardial cushion, still not fused with the ventral, to reach the summit of the interven-

tricular septum." It seems reasonable that in this area of embryologic fusion the conduction bundle will occupy a position along the postero-inferior aspect of the smaller defects, both simple interventricular septal defects and persistent atrioventricular canals.

In the case of a large interatrial septal defect, the atrioventricular bundle lay in close proximity to the atrial cavity, beneath the rim of rudimentary interatrial muscular septum. The position of the bundle might render it susceptible to injury during closure of the interatrial defect.

The atrioventricular node and bundle occupied normal positions in the case of a high interventricular defect in the muscular portion of the septum. The bundle coursed in close proximity to the membranous portion of the septum, which was intact.

In the case of complete transposition of the great vessels, the normal course of the conduction system perhaps could be predicted. In such an anomaly the embryologic defect involves the spiral septation of the truncus arteriosus, and the fusion of the ventricular septum and dorsal endocardial cushion remains undisturbed.

The course of the conduction system in the very large defects, such as common ventricle, remains unknown. In reporting such a case in 1925, Wilson and Grant⁶ were unable to demonstrate a true atrioventricular bundle. Preliminary studies on similar specimens in our laboratory have also failed to show an atrioventricular bundle comparable to those described in this report.

SUMMARY

Five hearts, demonstrating a variety of congenital defects were studied by serial sections, and the atrioventricular node and bundle were identified in each. In cases of membranous interventricular septal defect and atrioventricular canal, the atrioventricular bundle coursed along the postero-inferior margin of the ventricular defect in a subendocardial position. In a case of large interatrial septal defect, the atrioventricular node and bundle lay beneath a thin rim of rudimentary interatrial muscle. In cases of complete transposition and high

interventricular muscular septal defect the conduction system lay in the normal anatomic position.

ACKNOWLEDGMENT

The authors appreciate the cooperation of Drs. Dorothy H. Andersen and William A. Blanc of the Department of Pathology, Babies Hospital, who supplied the material used in this study. We also gratefully acknowledge the help of Miss Mary Dimitrakis in making the histologic preparations.

SUMMARIO IN INTERLINGUA

Cinque cordes con varie defectos congenite esseva studiate per sectiones serial. In omnes le nodo e le fasce atrioventricular esseva identificate. In casos de defecto membranose del septo interventricular e de canal atrioventricular, le fasce atrioventricular curveva al longo del margine postero-inferior del defecto ventricular in position subendocardial. In un caso de grande defecto del septo interatrial, le nodo e le fasce atrioventricular jaceva infra un tenue margine de rudimentari musculo interatrial. In casos de transposition complete e de defecto muscular del septo supero-interventricular, le systema de conduction occupava le position anatomic normal.

REFERENCES

- ¹ PURKINJE, J. E.: Mikroskopisch-neurologische Beobachtungen. Arch. f. Anat. Physiol. u. Wissenschaftliche Med. **12**: 281, 1845.
- ² HIS, W., JR.: Die Thätigkeit des embryonalen Herzens und deren Bedeutung für die Lehre von der Herzbewegung beim Erwachsenen. Arb. a. d. med. Klin. zu Le'pz. **14**, 1893.
- ³ DUSHAINE, J. W., KIRKLIN, J. W., PATRICK, R. T., DONALD, D. E., TERRY, H. R., JR., BURCHELL, H. B., AND WOOD, E. H.: Ventricular septal defects with pulmonary hypertension; surgical treatment by means of a mechanical pump-oxygenator. J.A.M.A. **160**: 950, 1956.
- ⁴ COOLEY, J. C., KIRKLIN, J. W., AND HARSHBARGER, H. G.: The surgical treatment of persistent common atrioventricular canal. Surgery **41**: 147, 1957.
- ⁵ WIDRAN, J., AND LEV, M.: The dissection of the atrioventricular node, bundle and bundle branches in the human heart. Circulation **4**: 863, 1951.
- ⁶ WILSON, J. G., AND GRANT, R. T.: A case of congenital malformation of the heart in an infant associated with partial heart block. Heart **12**: 295, 1926.

- ⁷ YATER, W. M.: Congenital heart block. *Am. J. Dis. Child.* **38**: 112, 1929.
- ⁸ —, LYON, J. A., AND McNABB, P. E.: Congenital heart block: Review and report of the second case of complete heart block studied by serial sections through the conduction system. *J.A.M.A.* **100**: 1831, 1933.
- ⁹ YATER, W. M., LEAMAN, W. G., AND CORNELL, V. H.: Congenital heart block: Report of the third case of complete heart block studied by serial sections through the conduction system. *J.A.M.A.* **102**: 1660, 1934.
- ¹⁰ WALLGREN, A., AND WINBLAD, S.: Congenital heart block. *Acta paediat.* **20**: 175, 1937.
- ¹¹ WENDKOS, M. H., AND STUDY, R. S.: Familial congenital complete A-V heart block. *Am. Heart J.* **34**: 138, 1947.
- ¹² TURPIN, R., LENÈGRE, J., AND CHASSAGNE, P.: Étude anatomo-clinique d'un cas de dissociation auriculo-ventriculaire, chez un nourrisson de 7 mois. *Arch. Franç. pédiat.* **4**: 617, 1947.
- ¹³ DONOSO, E., BRAUNWALD, E., JICK, S., AND GRISHMAN, A.: Congenital heart block. *Am. J. Med.* **20**: 869, 1956.
- ¹⁴ TRUAX, R. C., AND KAIN, J. A.: Conduction tissue of anomalous human hearts. *Anat. Rec.* **124**: 472, 1956.
- ¹⁵ WALLS, E. W.: The development of the specialized conducting tissue of the human heart. *J. Anat.* **81**: 93, 1947.

Neoss, A. J., and Litman, N. N.: Congenital Heart Block. *J. Pediat.* **48: 226 (Feb.), 1956.**

A baby girl born at term and normal except for a loud systolic murmur, had complete heart block with a ventricular rate of 50 per min. This was predicted 4 months before term by the attending obstetrician because the fetal heart rate was about 56 per minute. There had never been any other sign of fetal distress. The child has been followed for 2½ years, and the block remains. Administration of atropine in the neonatal period or at subsequent times failed to affect the block. It is thought that the child has an intraventricular septal defect. The previous literature on congenital heart block, and its usual cause, intraventricular septal defect, is reviewed.

HARVEY

Influence of an Oscillating Bed on Cutaneous Temperature and Oxygen Tension of Ischemic Toes

By CARLOS FORNO, M.D., HUGH MONTGOMERY, M.D., AND ORVILLE HORWITZ, M.D.

Measurements of temperature and oxygen tension of the skin demonstrated that treatment with an oscillating bed increases the circulation to ischemic toes. When the angle and duration of the dependent position of the foot of the bed were increased, further increments in circulation resulted.

THE effect of the dependent position upon blood flow to the extremities has long been a matter of controversy. Even when the limbs remain in the plane of the body, and the whole is tilted foot-downward, there is little agreement concerning the changes in blood flow that take place in the limbs. Youmans, Akeroyd, and Frank in 1935¹ found a rapid decrease in the temperature of the skin of the toes and of the lower legs when subjects were changed from the horizontal to the erect posture. The opposite result was obtained in 1938 by Roth, Williams, and Sheard,² who reported an increase in the temperature of the toes in 15 of 23 observations when the standing position was adopted. Studies utilizing a tilt table have given varying results, apparently depending upon the degree of downward inclination of the table. With 15 and 20 degrees of downward tilt, Roth and co-workers found an increase in the skin temperature of the toes. Nielsen et al.³ observed a rise in the skin temperature of the toes with 45 degrees downward inclination, although the skin temperature at other parts of the body was lowered. When the angle was 70 degrees the skin temperature of the toes decreased. Mayer-son and Toth⁴ observed a decrease in both the cutaneous and subcutaneous temperatures with a 75-degree foot-downward position. They thought that the difference in angles of inclination explained the divergence of their

results from those of Roth. Bridgen, Howarth, and Sharpey-Schafer,⁵ studied blood flow by venous occlusion plethysmography in subjects tilted from the horizontal to the vertical position, and found that flow decreased in a normal forearm but not in a sympathectomized limb. Similar results in the hand have been observed by Beaconsfield and Ginsburg.⁶ Williams, Montgomery, and Horwitz,⁷ by the polarographic method, found an increase in oxygen tension of the skin of the toes in normal, and especially in ischemic, limbs when the foot of a horizontal tilting table was lowered 7 inches (5 degrees), but no change in skin temperature was detected either in normal or ischemic toes.

Disagreement also exists about the measurements of blood flow in dependent limbs while the rest of the body is unchanged in position. Differences in method may in part account for this. Thus, Wilkins, Halperin, and Litter,⁸ by means of venous oxygen measurements, observed that blood flow to a dependent resting arm or leg of a subject in a recumbent position was greater than to the horizontal limb. Rosensweig⁹ also found an increase in flow, by the same method, in the dependent arm of the seated subject. Opposite results have been obtained by the method of venous occlusion plethysmography, in which the inherent difficulties, particularly "after drop," have long been recognized.¹⁰⁻¹⁵ Gaskell and Burton¹¹ reported a decrease in blood flow to the toes of a normal limb made dependent at the knee. Beaconsfield and Ginsburg¹² reported a decrease in flow in both normal and sympathectomized limbs. In recent studies

From the Vascular Section of the Edward Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.

This work was supported by a grant from the American Heart Association, Inc.

of some of the problems connected with the use of the venous occlusion plethysmograph, Allwood¹⁵ avoided making comparisons of blood flow in the dependent and horizontal positions measured by this method. Roddie¹⁶ used a calorimetric method, and his measurements suggest that the rate of blood flow through the fingertips is slightly greater and the peripheral resistance slightly less when the arm is dependent than when it is horizontal.

An oscillating bed allows a person to recline while the limbs remain in a constant position with respect to the body. It is in essence a mechanically driven tilting table supported at the center. It was designed in 1936¹⁷ and has been widely used in the treatment of ischemic limbs. Favorable clinical results after use of this bed have been reported, but very few measurements of its effect upon blood flow have been made. The cyclic changes create a complicated circulatory situation. The only studies we know of its effect on blood flow have been made by measurements of skin temperature. Barker and Roth in 1939¹⁸ were the first to evaluate the effect of this apparatus on ischemic limbs. They made a few measurements of the temperature of the toes of patients who had reduced blood flow to the lower limbs, usually, but not always, finding a slight increase after lowering the feet. Horton, Krusen, and Sheard¹⁹ found no change in the temperature of the toes of normal subjects directly attributable to the oscillating bed, and thought that the results of Barker and Roth were probably due to uncontrolled factors.

The purpose of the present study was to determine the effect of the oscillating bed on both the temperature and the oxygen tension of the skin of ischemic toes, and the part played by the degree and duration of downward inclination of the foot of the bed.

METHOD

An oscillating bed* permitting a wide range of

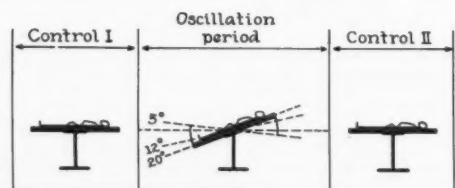


FIG. 1. Schema of oscillating bed, angles used, and sequence of the first series of experiments.

adjustment of angles and timing was used. The patients studied had arteriosclerosis obliterans of the lower limbs. In each patient the more ischemic foot was used, and the skin temperature and oxygen tension of the toes were measured on different days. Skin temperature studies were made in a constant temperature room with air 23 ± 1 C. Temperatures were recorded by a Brown potentiometer, 4 copper constantan thermocouples being placed at the base and 3 at the tips of the toes, and held in place by a single layer of adhesive tape. By means of the polarographic technique described by Montgomery and Horwitz²⁰ changes in cutaneous oxygen tension were measured in a room with a temperature of 24.5 to 30.0 C.; that during any one experiment varied by no more than 1 C. Four electrodes were inserted intracutaneously at the base of the toes. Percentage changes in oxygen tension were calculated from the changes in electric current. Skin temperature was recorded every 2 minutes and oxygen tension every 5 minutes except in the experiments in series IIb (table 1).

Series I. The first series of experiments was designed to establish the optimal oscillating pattern of the bed. Four patients, 2 male and 2 female, with arteriosclerosis obliterans were studied. Their ages ranged from 47 to 70 years. One was diabetic. None had ulcers or gangrene at the time the studies were made. A mean temperature of 27.2 C. (25.0 to 28.9 C.) was obtained in the skin of the tips of the toes after the patients' bodies were warmed in a constant temperature room at 20 C.

Eight skin temperature studies and 8 oxygen tension studies were made on each of the 4 patients (table 1). The patients were kept comfortably warm. The period of oscillation was always preceded and followed by a period in which the bed was immobile at the horizontal (fig. 1). The foot-up position was held at 5 degrees for 12 seconds. The foot-down positions were maintained 12 and 20 degrees for 12 seconds and for 1, 2, and 5 minutes. In any single experiment only 1 downward angle for 1 of the above periods of time was used. It took 27 seconds for the foot of the bed to move between the 5-degree foot-up angle and the 12-degree foot-down angle, and 40 seconds to

*We thank the J. H. Emerson Co., Cambridge, Mass. for the use of a Vasculaid Bed (Model V-R BSV, No. 1) for these experiments.

TABLE 1.—Changes in Temperature and Oxygen Tension of Skin of Toes of Patients on the Oscillating Bed

Series	Foot-down angles and timing	Temp. change tips of toes (°C.)				Temp. change bases of toes (°C.)				Oxygen tension change, bases of toes (%)			
		N	mean	t	p	N	mean	t	p	N	mean	t	p
I	Oscillating: 12°, 0.2 min.	12	+0.48	3.0	0.02	16	+0.09	1.1	0.3	15	-6	1.1	0.3
I	Oscillating: 12°, 1.0 min.	12	+0.55	1.1	0.3	15	+0.13	1.1	0.3	16	+17	2.2	0.05
I	Oscillating: 12°, 2.0 min.	10	+0.79	2.9	0.02	15	-0.21	0.8	0.5	13	+18	2.9	0.01
I	Oscillating: 12°, 5.0 min.	12	+1.10	6.6	0.001	15	+0.71	2.7	0.02	16	+16	3.7	0.003
I	Oscillating: 20°, 0.2 min.	11	+1.19	4.5	0.001	16	+0.63	4.2	0.001	16	+9	2.1	0.06
I	Oscillating: 20°, 1.0 min.	12	+0.22	2.3	0.05	16	-0.05	0.4	0.7	16	+31	3.0	0.01
I	Oscillating: 20°, 2.0 min.	12	+1.24	3.3	0.01	16	+0.46	1.2	0.3	16	+31	3.0	0.01
I	Oscillating: 20°, 5.0 min.	12	+2.08	8.9	0.001	16	+0.84	4.6	0.001	16	+31	2.4	0.03
Ia	Not oscillating: horizontal	—	—	—	—	16	+0.31	1.5	0.2	16	-9	2.1	0.06
Ib	Oscillating: Average of 5 readings taken after 5.0 min., 20° foot-down position, compared with average of 5 readings taken after intervening 2 min. foot-up position	—	—	—	—	—	—	—	—	7	+20	1.7	0.1
Ic	Not oscillating: 20°	5	+1.24	5.6	0.01	6	+1.32	8.1	0.001	16	+30	5.0	0.001
IId	Not oscillating: horizontal intermittent 33 mm. Hg venous occlusion in 5.0 min. cycles	—	—	—	—	—	—	—	—	8	-3	0.8	0.5

N=number of data; t=mean response/standard error, and p=probability that the mean change differs from zero due to random sampling variation only.

The oxygen tension changes, expressed as the ratio of the experimental period observation to the average control period observation, were subjected to a logarithmic transformation before statistical analysis. The mean responses have been converted back to per cent change in the table.

move between the 5-degree foot-up angle and the 20-degree foot-down angle.

When temperature of the skin was being measured, oscillation of the bed was started as soon as the skin temperature of the toes had stabilized. The first control period averaged 78 minutes, the experimental period 47 minutes, and the second control period 18 minutes. For the oxygen tension experiments 40 minutes were allowed for each of the 3 periods. The changes induced during any experiment were calculated by comparing the reading recorded at the end of the period of oscillation with the average of the readings obtained at the end of the 2 control periods. All results are reported as average changes.

Series II. The second series of experiments planned to clarify the details of the results of the first series, were of 4 types: (a) measurements with the bed horizontal, omitting the oscillating period, (b) measurements of the changes in skin temperature and oxygen tension during each cycle of the

oscillating bed, (c) measurements of the effect of the constant foot-down position without oscillation, and (d) learning the effect of venous pressure per se on the readings of the oxygen electrode. Cutaneous oxygen tension was recorded throughout all these experiments; some cutaneous temperatures were also recorded. In (a) the same patients were studied as in the first series of experiments; in (b), (c), and (d) some substitutions of patients were made, but all had previously been shown by vasodilatation test to have capacities for blood flow strictly comparable with those previously studied. Their range of skin temperature at full vasodilatation in a 20 C. constant temperature room was between 25.4 and 28.8 C.

RESULTS

General

All results are summarized in table 1. Since there was no significant relationship between

responses of toes of 1 foot and of all feet, when angles and timing were unchanged, responses of all toes are considered samples of a single population. The 3 types of response listed are the change in temperature of the skin of the tips of the toes, the change in temperature of the skin of the bases of the toes, and the per cent change in oxygen tension of the skin of the base of the toes.

Series I

The responses to the 20-degree dependent position are consistently and significantly more marked than to the 12-degree dependent position. For example, the greatest response in temperature of the tip of the toe to the 20-degree foot-down angle was significantly greater than the greatest response to the 12-degree angle ($p < 0.001$).

For a given angle, the temperature responses tend to increase as the time of dependency is increased, whereas the oxygen tension responses are about the same for all 3 cycle times greater than 12 seconds.

Of the combinations in series I, 20-degree dependency for 5 minutes produced the greatest response by all 3 types of measurement in which case the average increase in skin temperature of the tips of the toes represents an increase in blood flow to approximately 13 ml. per 100 ml. of tissue per minute from a control flow of 6 ml. per 100 ml. of tissue per minute.²¹

Series II

a. With the bed horizontal for 120 minutes, oxygen tension of the skin was measured throughout experiments on the 4 original patients. It decreased 9 per cent. Although this is not statistically significant ($p = 0.06$), it suggests a slightly lessened flow during prolonged horizontal immobility.

b. The separate effect upon oxygen tension of the foot-down and the foot-up part of each cycle was measured throughout experiments performed on 2 patients (1 a substitute). The 20-degree foot-down position was used for 5 minutes. The foot-up period was extended to 1 minute to provide time for all 4 electrodes

to be read. Each total cycle lasted 7 minutes; 5 cycles were studied in each experiment. In order to avoid variations in times of polarization of the electrodes, 3½ minutes were allowed to elapse between readings taken in the foot-up and in the foot-down positions. In all but 1 of the 10 cycles the oxygen tension was greater in the foot-down position than in the foot-up position. However, the degree of the effect differed widely in the 2 patients: in the first the mean oxygen tension in the foot-down position was 57 per cent greater than in the foot-up position, whereas in the second it was 2.8 per cent. The average of all the data is an increase of 20.3 per cent, which is not statistically significant.

c. The effects of a constant foot-down angle of 20 degrees without oscillation on 4 patients (1 a substitute) were measured in 11 experiments on skin temperature and 4 on oxygen tension. The duration of the experimental periods and of the preceding and succeeding control periods were the same as in the 20-degree angle experiments in series I. The skin temperature of the tips of the toes increased significantly ($p = 0.01$) as did the skin temperature at the base of the toes ($p = 0.001$); oxygen tension increased very significantly ($p = 0.001$). The results are in general similar to those from oscillations at 20-degree dependency for 5 minutes. However, the change in tip skin temperature was significantly smaller ($p = 0.01$), the change in base skin temperature was significantly greater ($p = 0.02$), and the oxygen tension change was about the same.

d. Whether dilatation of capillaries caused by increased venous pressure in the dependent foot might of itself affect oxygen electrode readings was studied in 3 patients (2 substitutes). Even though oxygen tension remained constant, we considered the possibility that an error might arise from a shortened diffusion distance from distended capillaries to electrode. In order to check this possibility the following experiment was performed. Each patient was kept in the horizontal position for 40 minutes. The increment of pressure that would result from a 20-degree tilt,

33 mm. Hg, was applied for 5 minutes by a cuff placed at the ankle, followed by a 5-minute period of release of pressure. Pressure was applied for a total of 12 times. Readings of oxygen tension were taken every 3 minutes throughout and no significant changes were observed during the application of pressure.

DISCUSSION

The factors involved are probably mainly those of hydrostatic pressures and vasomotor tone. When the body is tilted downward at the foot, there must be increments in arterial pressure at all points below the heart, and equal increments in the veins, unless venous valves close. As the veins fill, the valves open if they were closed, and the increment in hydrostatic pressure becomes equal in veins and arteries at any particular distance below the heart. If vasomotor tone is unchanged, a resulting dilatation of vessels decreases resistance, and flow increases even with an unchanged arteriovenous pressure difference. The increased flow continues until the foot is elevated, unless vasoconstriction should abolish the hydrostatic dilatation, and in our experiments it did not. If the valves do close during early dependency, there will be an increase in arteriovenous pressure difference until they again open, and this will contribute temporarily to an increase in flow. Such a rise in arteriovenous pressure difference would account for only a part of the measured increase in flow, because it would not explain the augmented flow as duration of dependency increases. More information about this might be gained from measurements of venous pressure, or by noting the flow of radiopaque substances in the veins.

When patients with severely ischemic limbs are treated on an oscillating bed, more than 1 minute of dependency at a 20-degree angle is required for the pink color of the foot to return. It is not surprising that the more prolonged foot-down positions resulted in the greater increments in temperature and oxygen tension.

Although the responses during 40 minutes

of continuous dependency at a 20-degree angle are marked, and comparable to those obtained during 40 minutes of oscillation to this angle with 5-minute foot-down, we have not studied this further. The oscillating bed has, when such a steep angle is used, the great clinical advantages over the constant foot-down position of avoiding hydrostasis, edema formation, and possible venous thrombosis. Previously, moderate increases in oxygen tension were demonstrated by using as small a constant foot-down angle as 5 degrees (7-inch elevation of the head of the bed), a constant foot-down angle that has less risk.⁷

The oscillating bed may have another advantage over the constant foot-down position; it may lessen the sludging of blood in ischemic limbs. If an ischemic limb is raised and then lowered, the time for return of color is greater than that in a normal limb that has the same vasomotor tone. If the procedure is then repeated, the time for return of color is less. This suggests that cyclic elevation and dependence has flushing action, combating a tendency to sludging.

Neither the interrupted closure method for measuring changes in oxygen tension nor the estimation of flow in skin by the temperature method lend themselves to repeated measurements during a single cycle of less than 2 minutes, and we did not attempt to analyze changes during such a short single cycle.

In our experiments changes in oxygen tension probably resulted for the most part from changes in blood flow, because changes in blood flow were usually demonstrable, the limbs were at rest and oxygen utilization is presumed to have been constant, and venous pressure per se of this order of magnitude seemed not to affect the readings of oxygen tension. In the venous pressure experiments, skin temperature was not measured, and it is possible that blood flow decreased and capillary permeability increased concomitantly. So, it may be that some of the oxygen tension of the tissue resulted from changes in capillary permeability, or from shortening of the oxygen gradient from capillaries to the electrode tip.

SUMMARY

Experiments were performed upon the ischemic feet of patients with occlusive arterial disease in order to learn whether an adjustable oscillating bed will increase blood flow as measured by an increase of the temperature of the skin of the toes and of cutaneous oxygen tension as estimated by the polarographic technic.

The effect of 2 angles of downward inclination, 12 and 20 degrees, and of various timings was studied. The greatest increase in the temperature of the skin of the toes and of cutaneous oxygen tension resulted after the greater angle and the most prolonged foot-down position of 5 minutes. These increases were significant at a probability of 0.05 or less. Intermittent venous occlusion had no significant effect on the oxygen tension.

It is concluded that the oscillating bed increases the flow of blood and the supply of oxygen to the ischemic foot if a considerable foot-down angle of the bed is maintained for a prolonged period during each cycle of the oscillation.

The clinical advantages of the oscillating bed over the constant foot-down position, in particular the avoidance of hydrostasis, edema formation, and possible venous thrombosis, are mentioned.

SUMMARIO IN INTERLINGUA

Esseva effectuate experimentos con le pedes ischemic de patientes con occlusive morbo arterial, con le objectivo de determinar si le uso de un regulabile lecto oscillante resulta in un augmento del fluxo de sanguine, mesurate como un altiamiento del temperatura cutanee in le digitos del pede e como un elevation del cutanee tension oxygenic (super le base de estimationes obtenite per medio del technica polarographic).

Le effecto de 2 differente angulos de inclination in basso—12 grados e 20 grados—e etiam le effecto de varie durationes esseva studiate. Le augmento maxime del temperatura cutanee del digitos del pede e del cutanee tension oxygenic resultava quando le plus grande del duo angulos e le plus grande prolongation del

abassation del pede—i.e. 5 minutas—esseva usate. Le effectos esseva significative con un probabilitate de 0,05 o minus. Intermittente occlusion venose habeva nulle effecto significative super le tension oxygenic.

Es formulate le conclusion que le lecto oscillante augmenta le fluxo de sanguine e le provision de oxygeno in un pede ischemic, providite que le angulo de abassamento del pede es considerabile e es mantenite durante un intervallo prolongate in le curso de omne cyclo de oscillation.

Es mentionate le avantages clinic del lecto oscillante in comparison con le abassation constante del pede. Istos include specialmente le evitation de hydrostase, de formation de edema, e possiblementemente de thrombosis venose.

REFERENCES

1. YOUMANS, J. B., AKEROYD, J. H., JR., AND FRANK, H.: Changes in the blood and circulation with changes in posture: The effect of exercise and vasodilatation. *J. Clin. Invest.* 14: 739, 1935.
2. ROTH, G. M., WILLIAMS, M. M. D., AND SHEARD, C.: Changes in the skin temperatures of the extremities produced by changes in posture. *Am. J. Physiol.* 124: 161, 1938.
3. NIELSEN, M., HERRINGTON, L. P., AND WINSLOW, C. E. A.: The effect of posture upon peripheral circulation. *Am. J. Physiol.* 127: 573, 1939.
4. MAYERSON, H. S., AND TOTH, L. A.: The influence of posture on skin and subcutaneous temperatures. *Am. J. Physiol.* 125: 474, 1939.
5. BRIDGEN, W., HOWARTH, S., AND SHARPEY-SCHAFER, E. P.: Postural changes in the peripheral blood flow of normal subjects: with observations on vasovagal fainting reactions as a result of tilting, the lordotic posture, pregnancy and spinal anesthesia. *Clin. Sc.* 9: 79, 1950.
6. BEACONSFIELD, P., AND GINSBURG, J.: The effect of body posture on the hand blood flow. *J. Physiol.* 130: 467, 1955.
7. WILLIAMS, P., MONTGOMERY, H., AND HORWITZ, O.: Oxygen tension of tissues by the polarographic method: VI. Effect of changes in position on oxygen tension of the skin of toes. *J. Clin. Invest.* 32: 1097, 1953.
8. WILKINS, R. W., HALPERIN, M. H., AND LITTER, J.: The effect of the dependent position upon blood flow in the limbs. *Circulation* 2: 373, 1950.
9. ROSENSWEIG, J.: The effect of arm position

- on the oxygen saturation of the effluent blood. *J. Physiol.* **127**: 11P, 1955.
10. ABRAMSON, D. I., ZAZEELA, H., AND MARRUS, J.: Plethysmographic studies of the peripheral blood flow in man: II. Physiologic factors affecting resting blood flow in the extremities. *Am. Heart J.* **17**: 206, 1939.
 11. GASKELL, P., AND BURTON, A. C.: Local postural vasomotor reflexes arising from the limb veins. *Circulation Research* **1**: 27, 1953.
 12. BEACONSFIELD, P., AND GINSBURG, J.: Effect of changes in limb posture on peripheral blood flow. *Circulation Research* **3**: 478, 1955.
 13. GASKELL, P.: The nature of the "after-drop" in the plethysmographic tracing during venous occlusion plethysmography with the veins distended. *J. Physiol.* **127**: 5P, 1955.
 14. —: The significance of the "after-drop" in venous occlusion plethysmography. *J. Physiol.* **131**: 627, 1956.
 15. ALLWOOD, M. J.: The "after-drop" in venous occlusion plethysmograms. *Circulation Research* **4**: 268, 1956.
 16. RODDIE, R. A.: The effect of arm position on the heat elimination from the fingers. *J. Physiol.* **127**: 11P, 1955.
 17. SANDERS, C. E.: Cardiovascular and peripheral vascular diseases. Treatment by a motorized oscillating bed. *J.A.M.A.* **106**: 916, 1936.
 18. BARKER, N. W., AND ROTH, G. M.: The treatment of occlusive arterial disease of the legs by means of the Sanders Vasocillator (Sanders Bed). *Am. Heart J.* **18**: 312, 1939.
 19. HORTON, B. T., KRUSEN, F. H., AND SHEARD, C.: An evaluation of methods and mechanical devices used in the treatment of peripheral vascular disease. *Arch. phys. Therap.* **22**: 389, 1941.
 20. MONTGOMERY, H., AND HORWITZ, O.: Oxygen tension of tissues by the polarographic method. I. Introduction: Oxygen tension and blood flow of the skin of human extremities. *J. Clin. Invest.* **29**: 1120, 1950.
 21. FELDER, D., RUSS, E., MONTGOMERY, H., AND HORWITZ, O.: Relationship in the toe of skin surface temperature to mean blood flow measured with a plethysmograph. *Clin. Sc.* **13**: 251, 1954.



Barratt-Boyes, B. G., and Wood, E. H.: The Oxygen Saturation of Blood in the Venae Cavae, Right-Heart Chambers, and Pulmonary Vessels of Healthy Subjects. *J. Lab. & Clin. Med.* **50**: 93 (July), 1957.

Because of the variability in oxygen saturation of venous blood within the normal heart, a method of withdrawing repeated blood samples in rapid succession through a cuvette oximeter, an instrument of high relative accuracy, has been developed for use during cardiac catheterization in an attempt to reduce the effects of incomplete mixing and changing cardiac output to a minimum. This presentation is an analysis of the data on oxygen saturation of blood obtained in this manner in an adequate series of unanesthetized, ambulatory, healthy, adult subjects. In addition to defining the mean and ranges of oxygen saturation within the right chambers of the heart and great vessels and the differences in the oxygen saturation of blood from these various sites, it has been possible to make some inference as to the relative importance of changes in cardiac output and laminar flow (incomplete mixing) on the variability of the values obtained at these various sites.

MAXWELL

The Nitrous Oxide Test

An Improved Method for the Detection of Left-to-Right Shunts

By ANDREW G. MORROW, M.D., F.A.C.S., RICHARD J. SANDERS, M.D.,
AND EUGENE BRAUNWALD, M.D.

The diagnosis of a left-to-right shunt generally depends upon the demonstration of significant differences in oxygen content among the venae cavae, the chambers of the right heart, and the pulmonary artery. The inconclusive or misleading results sometimes obtained with this method have stimulated interest in improved techniques. The wide arteriovenous difference that normally exists during the inhalation of nitrous oxide has been studied in the development of a more accurate diagnostic approach. The superiority of the nitrous oxide test over the oxygen method is demonstrated.

IN THE past, the detection of intracardiac and extracardiac left-to-right shunts has been based upon differences in the oxygen content of blood obtained from the venae cavae, right atrium, right ventricle, and pulmonary artery. Since relatively large differences in oxygen content may exist in these areas in subjects without shunts,^{1,3} the oxygen method sometimes provides inconclusive or even misleading diagnostic information. The inhalation of nitrous oxide, an inert foreign gas, and the subsequent measurement of its concentration in arterial and right heart blood provides a new diagnostic approach in which the difficulties inherent in the oxygen method are largely obviated. This communication presents the theory, technic, and diagnostic applications of the nitrous oxide test, and a comparison of the nitrous oxide and oxygen methods in the detection of left-to-right shunts. The clinical study to be presented is an extension of the technic devised and experimentally evaluated by Callaway.^{4,5}

Kety and Schmidt⁶ observed that immediately following nitrous oxide inhalation, cerebral tissue absorbed large quantities of the gas and a substantial arteriovenous difference existed until tissue saturation neared completion. Figure 1 demonstrates that a similar arteriovenous difference exists when

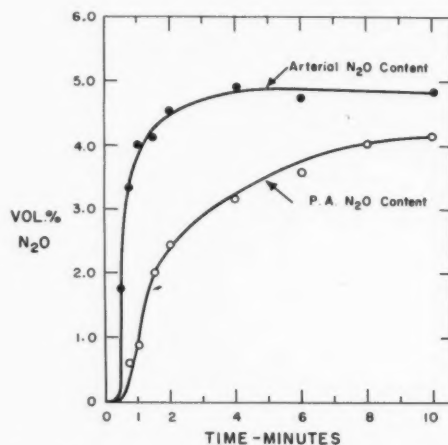


FIG. 1. Nitrous oxide levels in the femoral artery and pulmonary artery of a patient without a left-to-right shunt. Fifteen per cent nitrous oxide was inhaled for 10 minutes.

pulmonary artery blood is used instead of jugular vein blood. During the first minute of inhalation the concentration of nitrous oxide in right heart blood is low, since its appearance is delayed by tissue absorption. In the presence of a left-to-right shunt, blood from the left heart, rich in nitrous oxide, raises the level in right heart blood thereby making the detection of shunts possible.

MATERIAL AND METHODS

A total of 208 satisfactory nitrous oxide tests in 184 patients in whom the diagnosis was confirmed, forms the basis of this report. Most of

From the Clinic of Surgery, National Heart Institute, Bethesda, Md.

the patients were adults; 53 had left-to-right shunts, 43 at the atrial, 5 at the ventricular, and 5 at the pulmonary artery level. The diagnosis in the patients with shunts was established at operation in 29, by the passage of a catheter across the defect into the left heart in 19, and by retrograde thoracic aortography or dye-dilution studies with left heart injection in 5.⁷ The 131 control patients without shunts all had valvular rheumatic heart disease. This diagnosis was established by clinical examination as well as right and left heart catheterization.^{8,9} More than half of these patients were operated upon and the absence of a shunt was further confirmed. In all 53 patients with shunts and in 96 of the 131 patients without shunts right heart blood samples were analyzed for oxygen content.

Technic. Nitrous oxide tests were performed by placing the tip of a cardiac catheter in the right atrium, right ventricle, or pulmonary artery and a needle in a peripheral artery. Specimens for nitrogen blank determination were obtained before administration of nitrous oxide. The patient was instructed to breathe a mixture of 15 per cent nitrous oxide, 21 per cent oxygen, and 64 per cent nitrogen as deeply and as rapidly as possible. The gas was administered with a mask or mouthpiece and a Collins 3-way respiratory valve. Patients under general anesthesia were hyperventilated by manual compression of the breathing bag. Five- or 10-ml. blood samples were then simultaneously drawn at a constant rate from the right heart and peripheral artery during the 60 seconds of gas inhalation. Early in the series another sample proximal to any shunt was collected from the vena cava or a peripheral vein. As will be indicated, this sample was found unnecessary. A 10-minute period for desaturation was allowed when the test was to be repeated in another chamber. A double-lumen catheter was sometimes employed to shorten the procedure by sampling from 2 chambers simultaneously. Blood samples for oxygen analysis were obtained after the nitrous oxide tests had been completed. In general, 3 samples each were drawn from the pulmonary artery, right ventricle, and right atrium and 2 from each vena cava. In 40 of the 149 patients in whom specimens for oxygen content were obtained, the inferior vena cava could not be entered and in 10 patients pulmonary artery blood was not sampled. The oxygen contents to be presented in figure 4 represent the mean values of all specimens obtained in each site. The mixed vena caval oxygen content in the 109 patients in whom both caeae were entered was calculated by weighting the inferior caval values as twice the superior caval values.

Oiled, heparinized syringes were employed and air contamination was prevented with mercury-filled syringe caps. Nitrous oxide content was

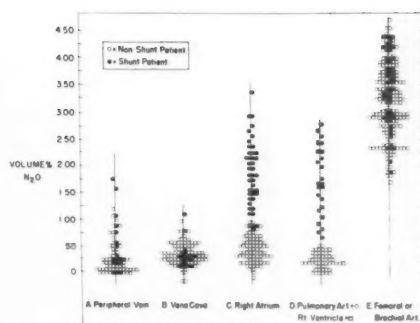


FIG. 2. Nitrous oxide samples from the venous system, right heart, and a peripheral artery in patients with and without left-to-right shunts. Nitrogen blank values have been subtracted.

determined by a modification of the Van Slyke manometric method.^{6,10} Oxygen contents were determined by the method of Van Slyke and McNeill.¹¹

RESULTS

Nitrogen Blanks. Since the manometric method does not distinguish dissolved nitrogen from nitrous oxide, blank samples are necessary to determine the nitrogen content of the blood prior to each nitrous oxide test. No systematic difference was found among nitrogen blank values in systemic artery, peripheral vein, or right heart blood in any given patient. The average of the 2 or 3 blank values in each patient was therefore used in all calculations. This average value for all patients ranged from 0.50 to 1.97 volume per cent with a mean of 1.30 ± 0.18 volume per cent. No difference in blank values existed between control patients and those with shunts. Six patients in whom the difference between simultaneous blanks exceeded 0.40 volume per cent were excluded from the study, since this large difference made sampling or analytic techniques suspect.

Nitrous Oxide Sample. The nitrous oxide sample, as used in this presentation, refers to the nitrous oxide content of the specimen less the blank value. In the control patients the range and scatter of nitrous oxide samples were widest in the peripheral vein and progressively narrowed as the pulmonary artery was reached (fig. 2).

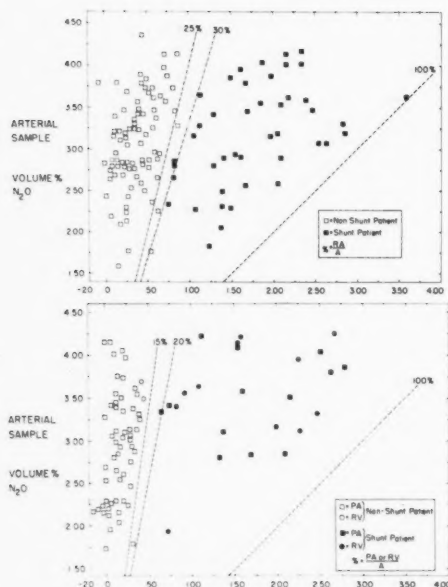


FIG. 3. *A, Top.* Relation between right atrial and arterial nitrous oxide samples in patients with and without left-to-right shunts. *Broken diagonal lines,* RA/A ratios. *B, Bottom.* Relation between pulmonary artery or right ventricular and arterial nitrous oxide samples in patients with and without shunts.

As would be anticipated, the patients with left-to-right shunts had peripheral venous and vena caval samples similar to the control patients (fig. 2 *A* and *B*). However, 39 of the 43 patients with shunts at the right atrial level had right atrial nitrous oxide samples between 1.06 and 3.39 volumes per cent. The highest right atrial sample among the control patients was 0.88 volume per cent. Thus, all but 4 of the patients with shunts had samples greater than the right atrial sample of any of the 83 control patients (fig. 2*C*). All 24 patients with shunts who had pulmonary artery or right ventricular tests had samples exceeding 0.64 volume per cent; the highest pulmonary artery or right ventricular sample of the 58 control patients was 0.47 volume per cent (fig. 2*D*). The systemic artery nitrous oxide samples ranged from 1.60 to 4.62 volumes per cent with a mean of 3.04 ± 0.59 volumes per cent. No systematic difference

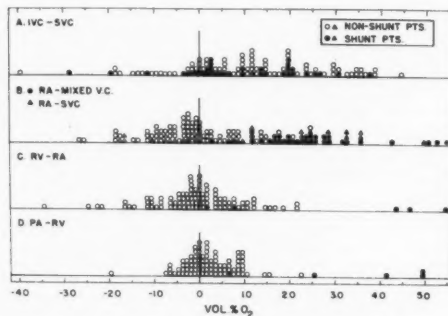


FIG. 4. Differences in oxygen content between right heart chambers and venae cavae in patients with and without shunts. *IVC (-) SVC* average = 0.94 ± 1.51 volume per cent (all patients). *RA (-) Mixed VC* average = $(-) 0.41 \pm 0.96$ volume per cent (non-shunt patients). *RV (-) RA* average = 0.01 ± 0.95 volume per cent (non-shunt patients). *PA (-) RV* average = 0.23 ± 0.53 volume per cent (non-shunt patients).

existed between the arterial nitrous oxide levels of patients with and without shunts (fig. 2*E*).

Relation between Arterial and Right Heart Nitrous Oxide Samples. In control patients high arterial nitrous oxide levels, reflecting better nitrous oxide uptake were, in general, associated with slightly higher right heart levels (fig. 3*A* and *B*). In patients with shunts the right heart nitrous oxide level distal to the shunt is determined to some extent by the venous level but primarily upon the quantity of shunted blood and its nitrous oxide content. Since the nitrous oxide content of shunted blood is identical to that of arterial blood, the ratio between right heart and arterial levels becomes meaningful and is therefore related to the magnitude of the shunt. In the 83 control patients, the ratio between right atrial and arterial samples ($RA/A \times 100$) was less than 30 per cent in all but 1, in whom it was 31 per cent. In 41 of the 43 patients with right atrial shunts the RA/A ratio was 30 per cent or more. The other 2 patients had ratios of 29 per cent (fig. 3*A*). In the 58 control patients with tests in the pulmonary artery or right ventricle the highest PA/A or RV/A ratio was 16 per cent. All 24 patients

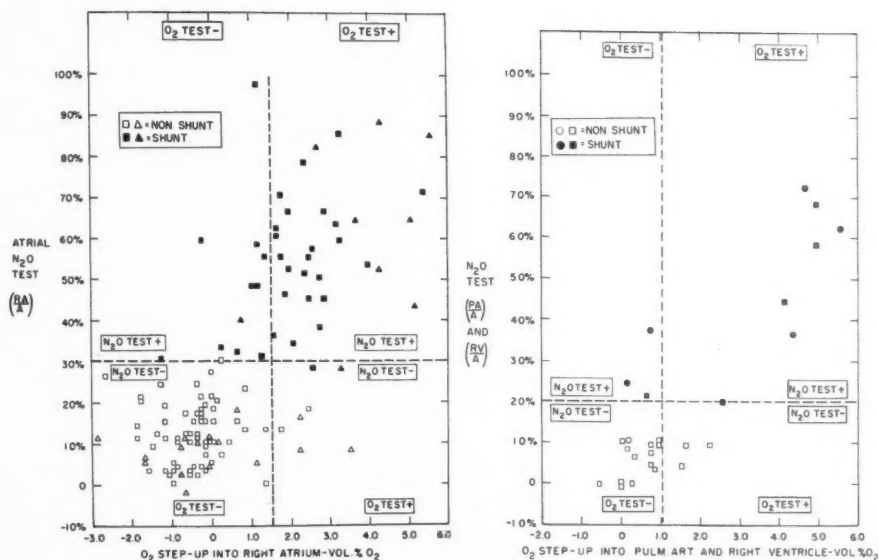


FIG. 5. *A, Left.* Comparison of oxygen differences with atrial nitrous oxide ratios in patients with and without left-to-right shunts in whom both tests were performed. *B, Right.* Oxygen differences compared with nitrous oxide ratios in the right ventricle or pulmonary artery in patients with and without shunts.

with shunts had a PA/A or RV/A ratio of 20 per cent or more (fig. 3B).

Oxygen Samples. Figure 4 presents the differences in oxygen content between contiguous sites of sampling. The oxygen content of inferior caval blood exceeded that of superior caval blood in 83 of 109 patients (fig. 4A). In control patients the range and scatter of oxygen content between consecutive cardiac chambers fell progressively as the pulmonary artery was reached. This range of difference was greatest between venae cavae and right atrium (fig. 4B). It diminished slightly between right atrium and right ventricle (fig. 4C), and was smallest between right ventricle and pulmonary artery (fig. 4D). These data confirm previous observations indicating incomplete mixing of blood in the cavae and right atrium.¹⁻³

In all but 1 of the 43 patients with left-to-right shunts at the atrial level the oxygen content of right atrial blood exceeded that of vena caval blood. However, in 11 of these 43 patients the oxygen content of right atrial

blood did not exceed that of caval blood by 1.5 volumes per cent or more. Among 93 control patients 6 had a right atrial blood oxygen content exceeding caval content by 1.5 volumes per cent or more (fig. 4B). Two of the 5 patients with left-to-right shunts at the right ventricular level and 1 of the 5 patients with shunts into the pulmonary artery did not have oxygen differences exceeding 1.0 volume per cent (fig. 4C). Among 94 control patients, 11 had increases of 1.0 volume per cent or more between the right atrium and right ventricle and 4 of 86 controls had increases of this magnitude between the right ventricle and pulmonary artery.

Comparison between the Oxygen and Nitrous Oxide Methods. In figure 5A the differences in oxygen content between vena caval and right atrial blood have been plotted against the nitrous oxide RA/A ratios in the 122 patients in whom both tests were performed. For purposes of comparison, an oxygen increase of 1.5 volumes per cent between the caval and right atrial blood and an RA/A

ratio of 30 per cent have been employed as standards for the diagnosis of a shunt at the atrial level. With these criteria there were 5 false positive tests with the oxygen method and 1 false positive test with the nitrous oxide method in the 79 control patients. In the 43 patients with proved shunts at the atrial level there were 11 false negative tests with the oxygen method and 2 false negative nitrous oxide tests. Thus, the oxygen method resulted in 16 diagnostic errors and the nitrous oxide method in 3.

It is also apparent from figure 5A that all 3 diagnostic errors in the nitrous oxide tests occurred in patients with RA/A ratios between 29 and 31 per cent, close to the diagnostic level set at 30 per cent. In contrast, 9 of the 15 diagnostic errors in the oxygen method occurred in patients in whom the oxygen differences were more than 0.5 volume per cent from the somewhat arbitrary diagnostic line. A difference of 1.5 volumes per cent was selected because it is the standard generally accepted and represented a judicious balance between false positive and false negative oxygen results. It may be noted that if an oxygen increase of 1.0 volume per cent had been employed as the diagnostic criterion there would be a total of 13 diagnostic errors, and if 2.0 volumes per cent was chosen, there would be 22 errors.

In figure 5B the differences in oxygen content between right atrial and right ventricular blood and between right ventricular and pulmonary artery blood are plotted against the nitrous oxide ratios in the 27 patients who had both tests. Diagnostic criteria selected for these areas were an oxygen increase of 1.0 volume per cent or more and an RV/A or PA/A ratio of 20 per cent or more. In the 17 control patients there were 3 false positive tests with the oxygen method and none with nitrous oxide. In the 10 patients with shunts there were 3 false negative tests with the oxygen method and none with nitrous oxide. Thus, in these 27 patients the oxygen method resulted in 6 diagnostic errors and the nitrous oxide test in none.

DISCUSSION

Errors in the performance of the nitrous oxide test relate to the administration and uptake of the gas as well as to the collection and chemical analysis of the blood samples. An adequate uptake of nitrous oxide is essential but may be prevented by a large leak around the mouthpiece, hypoventilation, or severe pulmonary parenchymal disease. When the test is performed in an anesthetized patient, the anesthesiologist must provide hypoventilation and of course cannot employ nitrous oxide as the anesthetic agent prior to the test.

Small differences in the nitrous oxide content of superior caval, inferior caval, and coronary sinus blood and incomplete mixing of these streams in the right atrium introduce an element of variability into the results of the test. However, this source of error is not so great as in the oxygen method, since the differences in the oxygen content of the right atrial tributaries are greater than the variations in their nitrous oxide content.

An important potential source of error is improper positioning of the catheter. When the test is performed in the right atrium, the catheter tip must be placed close to the tricuspid valve to insure that the sample will be drawn from an area distal to the entrance of any shunt at this level. Should the catheter inadvertently be passed through a defect into the left atrium, a nitrous oxide sample equal to the arterial will be obtained. Another test in the pulmonary artery or right ventricle will indicate whether a true atrial septal defect exists or whether the catheter passed through a nonshunting patent foramen ovale.

Contamination of the blood samples by air and excessive suction on the sampling syringe should be avoided, since either can falsely lower the nitrous oxide content of the sample. Blood must be drawn at a constant rate during the sampling period, since both the arterial and venous nitrous oxide contents are changing throughout this period (fig. 1). The difference between duplicate Van Slyke nitrous oxide determinations in this laboratory

is ordinarily less than 0.10 volume per cent.

Since the errors inherent in the technics of sampling and analysis are independent of the arterial nitrous oxide level, they assume greater significance when the ratio is calculated with a low arterial sample. For example, an error of 0.20 volume per cent in a right heart sample represents 10 per cent of an arterial level of 2.00 volumes per cent, but only 5 per cent of an arterial level of 4.00 volumes per cent. Fifteen nitrous oxide tests were eliminated from the series because of arterial levels less than 1.50 volumes per cent. Seven of these unsatisfactory tests were attributed to hypoventilation. The other 8 tests were performed in cyanotic patients with right-to-left shunts. In these patients pulmonary venous blood, with a high nitrous oxide level, was presumably diluted by right heart blood with a low level and thereby lowered the arterial content. Thus, in the presence of a large right-to-left shunt, the arterial nitrous oxide content may not accurately reflect the content of blood that has been shunted from left to right. Therefore, the right heart arterial nitrous oxide ratio (fig. 3) can no longer be relied upon. However, in such circumstances, the absolute level of nitrous oxide in right heart blood (fig. 2) may still be useful in the detection of left-to-right shunt.

The vena caval and peripheral venous nitrous oxide samples were originally obtained for comparison with the sample from the right heart, much as caval and right atrial oxygen contents are compared. However, it was apparent that in the absence of a shunt the nitrous oxide content of right atrial blood was relatively constant and less than 30 per cent of the arterial content (fig. 3). When this maximum value had been established, it was no longer necessary to sample the cava or peripheral vein. Furthermore, the inclusion of caval and peripheral venous samples did not improve the diagnostic accuracy of the method.

The superiority of the nitrous oxide test over the oxygen method, as demonstrated in

figure 5, is related to several factors. The oxygen content of right heart blood varies markedly among different individuals and in the same subject at different times. Therefore, blood proximal to any shunt must always be sampled. This may lead to errors in the diagnosis of atrial septal defects because caval blood is poorly mixed and laminar flow is present, particularly from the renal veins.¹² The sampling of renal vein blood with its high oxygen content may mask the presence of a shunt into the right atrium. In some patients the catheter cannot be passed into the inferior vena cava. It has been demonstrated (fig. 4A) that the oxygen content of superior caval blood is generally lower than inferior caval blood. Hence, a comparison of superior caval and atrial blood could lead to the false diagnosis of an atrial shunt. In 3 of the 5 false positive oxygen tests only the superior cava could be sampled (fig. 5A). Further error in the oxygen method is introduced by the variations in the patient's physiologic state that occur during the time required for complete sampling. This source of error is also obviated with the nitrous oxide tests, since the 2 samples required are drawn simultaneously. An added practical advantage of the nitrous oxide over the oxygen method is that fewer samples and analyses are necessary.

Modifications of the nitrous oxide test involving different gas concentrations, sampling periods, and ventilatory states are being investigated. The test may be further improved by the use of other inert gases that are presently being evaluated. Since it is apparent that the nitrous oxide ratio is a function of the contribution of the shunt to total pulmonary flow, consideration is being given to the application of nitrous oxide in the quantitation as well as the detection of left-to-right shunts.

DIAGNOSTIC CRITERIA

The diagnostic criteria currently employed in the application of the nitrous oxide test may be summarized. In the right atrium,

an RA/A ratio above 30 per cent is considered diagnostic of a shunt. An RA/A ratio below 25 per cent indicates the absence of a shunt; ratios between 25 per cent and 30 per cent are considered inconclusive. A PA/A or RV/A ratio above 20 per cent is diagnostic of a shunt, while the absence of a shunt is indicated by a ratio below 15 per cent. Pulmonary artery or right ventricular tests with ratios between 15 per cent and 20 per cent are considered inconclusive. An arterial level of at least 1.5 volumes per cent is necessary for a valid test.

SUMMARY

An improved method for the detection of left-to-right cardiac shunts is presented. Fifteen per cent nitrous oxide is inhaled for 1 minute while integrated blood samples are drawn simultaneously from the right heart and a systemic artery. The technic, diagnostic criteria, and sources of error of this method are presented in detail.

In 41 of 43 patients with proved shunts at the atrial level, the ratio of right atrial to arterial nitrous oxide content (RA/A) exceeded 31 per cent, the highest value observed in 83 control patients. In all 24 patients with proved shunts the ratio PA/A or RV/A exceeded 20 per cent. The highest PA/A or RV/A ratio in 58 patients without shunts was 16 per cent.

The nitrous oxide test was demonstrated to be distinctly superior to the oxygen method. In 149 patients in whom both tests were performed, there were 22 diagnostic errors on the basis of oxygen differences and 3 errors with the nitrous oxide test.

SUMMARIO IN INTERLINGUA

Es presentate un meliorate methodo pro le detection de derivation cardiac sinistrodextere. Oxygen nitrose in un concentration de 15 pro cento es inhalate durante 1 minuta, e simultaneemente specimens de sanguine integrate es obtenite ab le corde dextere e ab un arteria systemic. Le technica, le criterios

diagnostic, e le causas de error in iste methodo es presentate in detalio.

In 41 ex 43 patientes con demonstrate derivationes al nivello atrial, le proportion inter le oxydo nitrose dextero-atrial e le oxydo nitrose arterial excede 31 pro cento (le valor maximal observate in 83 patientes de controlo). In 24 ex 24 patientes con demonstrate derivationes le proportion inter le oxydo nitrose pulmono-arterial e le oxydo nitrose arterial o inter le oxydo nitrose dextero-ventricular e le oxydo nitrose arterial excede 20 pro cento. (Le valor maximal observate in 58 patientes sin derivationes esseva 16 pro cento.)

Le test a oxydo nitrose se monstrava claramente superior al methodo a oxygeno. In 149 patientes in qui ambe tests esseva executate, 22 errores diagnostic haberea resultate del test a oxygeno, 3 del test a oxydo nitrose.

REFERENCES

1. Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. D., and Richards, D. W.: Measurement of cardiac output in man, using the technique of catheterization of the right auricle or ventricle. *J. Clin. Invest.* **24**: 106, 1945.
2. Warren, J. V., Stead, E. A., Jr., and Branston, E. S.: The cardiac output in man: A study of some of the errors of right heart catheterization. *Am. J. Physiol.* **145**: 458, 1946.
3. Dexter, L., Haynes, F. W., Burwell, C. S., Eppinger, E. C., Sageron, R. P., and Evans, J. M.: Studies of congenital heart disease: II. *J. Clin. Invest.* **26**: 554, 1947.
4. Morrow, A. G.: New methods in the diagnosis of interatrial septal defects. Cardiovascular Surgery, International Symposium at the Henry Ford Hospital. Philadelphia, W. B. Saunders Co., 1955, p. 345.
5. Callaway, J. J.: Atrial septal defects: The use of nitrous oxide in the diagnosis. To be published.
6. Ketty, S. S., and Schmidt, C. F.: Determination of cerebral blood flow in man by use of nitrous oxide in low concentrations. *Am. J. Physiol.* **143**: 53, 1945.
7. Braunwald, E., Tanenbaum, H. L., and Morrow, A. G.: Dye-dilution curves from left heart and aorta for localization of left-right shunts and detection of valvular in-

- sufficiency. *Proc. Soc. Exper. Biol. & Med.* **94**: 510, 1957.
8. ROSS, J., JR., BRAUNWALD, E., AND MORROW, A. G.: Clinical and hemodynamic observations in pure mitral insufficiency. *Am. J. Cardiol.* In press.
9. MORROW, A. G., BRAUNWALD, E., HALLER, J. A., JR., AND SHARP, E. H.: Left heart catheterization by the transbronchial route: Technique and applications in physiologic and diagnostic investigations. *Circulation* **16**: 1033, 1957.
10. KETY, S. S.: Quantitative determination of cerebral blood flow in man. *Methods in Med. Res.* **1**: 204, 1950.
11. VAN SLYKE, D. D., AND MCNEILL, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. *J. Biol. Chem.* **61**: 523, 1924.
12. SIROTA, J. H., AND GORDON, A. J.: Method to measure regional contributions to total cardiac output in man with observations on laminar flow in the great veins. *J. Appl. Physiol.* **6**: 485, 1954.



Surawicz, B., Braun, H. A., Crum, W. B., Kemp, R. L., Wagner, S., and Bellet, S.: **Clinical Manifestations of Hypopotassemia.** *Am. J. M. Sc.* **233**: 603 (June), 1957.

The frequency of signs and symptoms of hypopotassemia was investigated in relationship to plasma potassium levels with evaluation of the clinical status of the patients before and after administration of potassium salts. During a 7 month period 557 cases manifesting hypokalemia were encountered in 2786 potassium determinations. The incidence of plasma potassium levels below 3.5 mEq. per liter was higher in females (22 per cent) than in males (18.3 per cent). The mortality of patients with hypopotassemia was 49 per cent compared to that of the total hospital fatality rate of 15 per cent. Fifty patients were selected for detailed study of serum electrolytes, causes of depletion and other clinical features. Among the disorders associated with potassium depletion, hepatic cirrhosis headed the list. Inadequate diet, infusion of potassium-free solutions, vomiting or gastrointestinal suction, diarrhea and renal disease were factors operating to lower the plasma potassium levels. Patients with the lowest potassium levels also had the lowest concentrations of chlorides and calcium and were more often alkalotic. The clinical abnormalities encountered in these patients were of the type seen in seriously ill patients with or without hypopotassemia. In order to determine which signs and symptoms were attributable to potassium deficiency, a rapid infusion of potassium was employed. The most significant changes accompanying infusion were improved mental status and increased peristaltic activity. A decrease in activity of deep tendon reflexes showed some correlation with the decrease in plasma potassium levels. The nonspecific nature of the clinical aspects of hypopotassemia in seriously ill patients is emphasized indicating the importance of electrocardiographic and electrolyte determinations in the diagnosis of this disorder.

SHUMAN

CLINICAL PROGRESS

Anesthesia in Patients with Heart Disease

By LEROY D. VANDAM, M.D., AND THOMAS K. BURNAP, M.D.

THE consensus among internists, surgeons, and anesthesiologists today is that patients with heart disease fare well when anesthetized. Although this is primarily a clinical impression, there is a growing volume of literature to support this thesis. One must distinguish, however, between patients with heart disease who are undergoing surgery on other organ systems and those who are to undergo cardiac surgery itself. It is not easy to gather data on this subject because of the difficulty in comparing anesthetic morbidity and mortality in like groups of patients. For example, one clinic might examine the results of an anesthetic technique employed for mitral valvuloplasty and find no mortality, whereas another group might find the mortality to be 15 or 20 per cent. The explanation for this difference probably would be that in the first report the individuals anesthetized and operated on had relatively benign mitral stenosis while in the second, the patients might have fallen into a group IV functional classification.¹ Thus the first consideration in evaluating the effects of anesthesia must be the severity of the heart disease.

In discussing anesthetic agents and techniques it is well to remember that usually it is the skill with which an anesthetic is given rather than the choice of a particular agent that determines the safety of the procedure. Likewise the other phases of the operation are just as important as the anesthetic in the outcome. It should not be forgotten that anesthesia is but a small part of the total surgical experience.² The patient with heart

disease often undergoes a relatively long period of medical preparation. Before operation he may be beset with great anxiety. Preoperative medication is given to counteract this. Immediately prior to operation there is starvation and then the administration of the anesthetic. The patient then undergoes a surgical procedure that has many consequences from the standpoint of the postoperative course. Finally, after anesthesia and operation are over, there are many natural bodily responses to that which has gone before. Among these various things it may be very difficult to discern the deleterious effects of the anesthetic agent or technique.

It is the purpose of this brief review to delineate some of the factors in the total operative experience that may contribute to anesthetic morbidity and mortality. We shall discuss the role of preoperative preparation, of preanesthetic medication, of the anesthetic agent and technique, and the operation itself in the problems that are encountered during anesthesia. An understanding of these matters enables the internist to prepare his patient for anesthesia and operation rationally.

MEDICAL PREPARATION OF THE PATIENT

The very drugs that are employed to bring the patient into the best possible state before operation are often the ones that create difficulty during anesthesia. The use of digitalis is perhaps the best example. It is well known that it is difficult to achieve just the right amount of digitalization in the very ill cardiac patient.³ Inadequate or "overdigitalization," not previously recognized, will pose considerable problems for the anesthesiologist. If a patient is on the verge of toxicity, it requires just a little extra stress during induction or maintenance of anesthesia to produce

From the Division of Anesthesia, Department of Surgery, Peter Bent Brigham Hospital and Harvard Medical School, Boston, Mass.

increasing degrees of heart block, serious ventricular arrhythmias, and even cardiac arrest. Induction of anesthesia may be likened to the effect of any stress, such as exercise, in revealing digitalis toxicity. Despite the best preparation and management as far as anesthesia is concerned, respiratory obstruction, excitement, and breath-holding may precipitate the difficulties enumerated above. Perhaps the most unpredictable patient in this regard is the patient who is "digitalized" just the day before operation. It hardly seems possible that adequate digitalization, enough to withstand the stresses of anesthesia and operation, can be accomplished in such a short period of time.

In the case of inadequate digitalization the prospect of rapid heart rates, cardiac failure, and pulmonary edema looms large. This is one reason why, prior to anesthesia, one tries to counteract anxiety as much as possible to avoid a rapid heart rate that may precipitate pulmonary edema. In the seriously ill cardiac patient who has been given digitalis, electrocardiographic monitoring throughout the course of anesthesia and operation seems almost mandatory. If a tachycardia or arrhythmia is observed, one needs the electrocardiogram for accurate diagnosis and to choose the appropriate drug for treatment.

Although we have written mainly about digitalis, it should be also pointed out that quinidine, procaine amide, the prior use of cortisone, serpasil, chlorpromazine, and anti-hypertensive drugs, all make the administration of anesthesia more hazardous by the production of arrhythmias and hypotension.^{4, 5}

Another factor in the development of arrhythmias or hypotension during induction and maintenance of anesthesia is the practice of instituting vigorous diuresis prior to surgery in order to secure a "dry" body weight. Vigorous diuresis may not only lower the blood volume but may lead to electrolyte imbalance, particularly with regard to sodium and potassium,⁶ so that hypotension and serious cardiac arrhythmias may ensue. The combinations of digitalis, electrolyte imbal-

ance, and the effects of anesthetic agents on the circulation are so interrelated that it is surprising that more arrhythmias and hypotension are not seen.

PREANESTHETIC MEDICATION

It is the purpose of preanesthetic medication to maintain the patient in good condition by allaying apprehension and to counteract some of the undesirable effects of anesthesia, such as increased salivary secretions and untoward vagal effects on the heart. The most commonly used premedicants are the barbiturates, the analgesics, and the belladonna derivatives. One can never be certain, however, that the preanesthetic medications used may not exhibit their not uncommon side effects.

The opiates and synthetic analgesics are particularly prone to cause hypotension in the good risk and even more so in the cardiac patient. It has been shown by many that hypotension following their use is due to a combination of effects on central regulating mechanisms in the medulla, on myocardial contractility, and on smooth muscle peripherally.⁷ If a normal individual will faint on a change in position after the administration of morphine or meperidine (Demerol), one can easily predict the effect in the cardiac patient when he is transported to the operating room, moved from litter to operating table, and then placed in an unusual position on the operating table. Morphine and the other analgesics are needed for patients in pain and for the safe conduct of some anesthetic techniques. Their side effects, however, must be anticipated. Many patients have undergone cancellation of operation prior to the administration of anesthesia because of the hypotensive effect of these drugs.

Atropine or its congeners are used commonly to inhibit salivary secretion and to block untoward vagal influences on the heart during anesthesia and operation. A small quantity of atropine will inhibit salivary secretions. Scopolamine will accomplish this even better. When the problem is inhibition of the cardiac vagus, however, one encounters difficulty with the cardiac patient. The quan-

tity of atropine needed to block the vagus adequately is often unsafe for the heart patient in that tachycardia and hypotension may be produced. If a patient is satisfactorily digitalized and the heart rate is slow, the administration of atropine may increase the pulse rate to hazardous levels. Large doses of atropine in addition to the muscarinic-blocking on the heart interfere also with ganglionic transmission in the autonomic nervous system. Thus the patient given a large dose of atropine may also evidence postural hypotension.⁸

In the prevention of tachycardia a possible side effect of meperidine on cardiac rate must be considered. This drug, which is a good analgesic and similar in most respects to morphine, has the additional property of producing vagal block. There have been instances wherein the use of meperidine has precipitated a rapid atrial rate and heart failure when given to patients with slower rates and atrial flutter.⁹

These details about preanesthetic medication are mentioned to emphasize their possible untoward effects in the cardiac patient who is about to undergo anesthesia. These drugs can and must be used with caution. In moderate dosage the barbiturates are safest for avoidance of apprehension. The interaction of the tranquilizing and anesthetic drugs has already been noted to produce undesirable side effects.⁵ Reserpine (Serpasil) because of the slow rate of excretion must be discontinued many days before anesthesia lest hypotension supervene. Atropine, unless employed for the treatment of patients with complete heart block, should be used sparingly for the effect on salivary secretion. The same precautions apply to the employment of morphine or meperidine unless they be needed for the relief of pain.

ANESTHETIC AGENTS

All of the potent general anesthetic agents exhibit effects in common on the cardiovascular system. These agents are di-ethyl ether, cyclopropane, chloroform, di-vinyl ether,

ethyl chloride, and some of the newer fluorinated compounds. While ether and cyclopropane are used most frequently, it should be understood that all these agents decrease myocardial contractility in direct proportion to the blood level of anesthetic achieved. Ordinarily hypotension is not perceived during anesthesia because of various compensating vascular reflexes. The effect on cardiac output of these agents is best seen in the heart-lung preparation where such reflexes are not brought into play.¹⁰ However, the deeper the level of anesthesia the more frequently is hypotension seen: particularly so in the patient with heart disease. Despite opinion to the contrary, overdosage with di-ethyl ether is a frequent cause of hypotension. According to experiments in the dog, were it not due to a coincident reflex release of epinephrine and norepinephrine during di-ethyl ether anesthesia, this commonly observed hypotension would be almost universally seen.¹¹

Because the anesthetist knows that hypotension accompanies the use of potent inhalational agents, he has adopted techniques that allow him to use these agents sparingly. It is not uncommon in operations on the heart, for example, to administer di-ethyl ether so that the patient is maintained in the first stage of anesthesia, the stage of analgesia.¹² Such light anesthesia avoids the depressant effect on the cardiac output of greater blood levels of anesthetic. The patient experiences no pain and can frequently respond to simple commands. In the postoperative period he will have little recollection for the events during operation. Similarly the use of the muscle relaxants has enabled one to use the weaker general anesthetic agents, nitrous oxide and ethylene, with high concentrations of oxygen for the performance of major surgery. Generally all that is required of anesthesia for a major surgical procedure is a combination of analgesia, amnesia, and muscle relaxation. Analgesia and amnesia usually can be attained by the inhalation of mixtures of 70 per cent nitrous oxide in oxygen combined with the intravenous injection of one of the muscle relaxants, so that the sur-

geon encounters muscle relaxation and has ready access to the field.

Other common effects of the general anesthetic agents involve the peripheral vasculature. A most striking effect after the onset of general anesthesia is the rapid appearance of vasodilatation in the skin. This vasodilatation is shared by skeletal muscle and is equivalent to that which might be obtained from a chemical or surgical sympathectomy.¹³ In other words, the blood flow to the extremities increases as much as 4 times early in the course of anesthesia. Were it not for compensatory vasoconstriction in other vascular beds, arterial hypotension would be encountered frequently. When vasodilatation in the extremities is greatest, vasoconstriction in the liver and kidneys has been found. The cerebral and coronary circulations are not involved in this compensatory vasoconstriction. Just why vasodilatation in the skin and muscles takes place is not clear at present. As anesthesia is continued, however, vasodilatation in the periphery disappears and the hepatic and renal circulations are restored toward normal. Appreciation by the anesthetist of these circulatory alterations has done much to eliminate the hazards of general anesthesia.

ANESTHETIC TECHNIC

It may seem trite to say that in the last analysis all patients, especially those with heart disease, encounter trouble during anesthesia because of anoxia. Anoxia, as in waking life, is related either to respiratory or circulatory deficiency. Frequently one cannot distinguish between the two. Failure to give oxygen or to relieve respiratory obstruction during anesthesia is just as hazardous as arterial hypotension. If anoxia is the basic fault, it follows that patients with pre-existing difficulty in coronary arterial perfusion are those who will suffer most under faulty anesthetic management. Consequently, the patient with coronary arterial disease or aortic valvular disease, is the one who will tolerate anoxia least. Similarly patients who are apt to die suddenly in waking life are

those who will expire in the advent of anesthetic difficulty. Thus, people with complete heart block and Stokes-Adams attacks,¹⁴ and patients prone to the development of acute tachycardias and arrhythmias are serious problems in anesthesia. Good anesthetic management lies in the understanding of the pathologic physiology of the patient's heart disease.

Anoxia and hypotension should be avoided during anesthesia in the patients with heart disease. This is sometimes more easily said than done. Oftentimes hypoxia and hypotension intervene despite the best anesthetic management. The discussion that follows will attempt to point out a few of the many factors other than faulty technic that lead to anoxia and hypotension during anesthesia.

The manner in which anesthetic technic may create difficulties for the cardiac patient may be seen in the situations of inadequate pulmonary ventilation, intubation of the trachea, and the appearance of cough.

Adequate pulmonary ventilation is necessarily part of good anesthetic technic. Unfortunately practically every anesthetic agent and adjunct interferes in some way with normal respiration. Preanesthetic medication, whether barbiturate or opiate, may depress the response of the respiratory center to carbon dioxide. The general anesthetic agents also depress the response of the respiratory center. Were it not for stimulatory peripheral respiratory reflexes, respiratory depression would be seen even with di-ethyl ether. The muscle relaxants interfere with respiration at the periphery through a blocking effect on neuromuscular conduction. The severity of the respiratory problem may be enhanced by an open thorax or certain operative positions such as the lateral decubitus and Trendelenburg. These factors are noted to illustrate the complexity of the respiratory problem in anesthesia. There are few practical monitoring devices to warn the anesthetist that pulmonary ventilation is inadequate.

The end result of inadequate pulmonary ventilation is always anoxia and carbon di-

oxide accumulation. Oxygenation is more easily maintained than the elimination of carbon dioxide. Consequently, respiratory acidosis has loomed large in the explanation of some of the untoward circulatory effects of anesthesia. Increased blood levels of carbon dioxide decrease myocardial contractility, predispose the heart to vagal influence, and may be the reason for the development of certain ventricular arrhythmias and arterial hypotension seen during or at the conclusion of anesthesia.

If one examines the circumstance during which cardiac arrest occurs most frequently during anesthesia, it will be found that tracheal intubation is often a precipitating event. It has been assumed that stimulation of the trachea gives rise to vagal stimulation with consequent cardiac inhibition. This has been called a vago-vagal reflex. However, this is not the customary response. Ordinarily during intubation of the trachea if there is adequate oxygenation and a satisfactory depth of anesthesia, the response to tracheal stimulation is that of tachycardia and hypertension.¹⁵ Seemingly a sympathetic rather than a vagal response is elicited. This can be confirmed by anyone who observes the electrocardiogram during intubation. Nevertheless tachycardia and hypertension may place considerable strain on an already diseased heart. Ideal conditions, technical facility, and the appropriate level of anesthesia can minimize these sympathetic effects.

Coincident anoxia or carbon dioxide retention determines the response to tracheal intubation. Vagal effects similar to those ordinarily seen in other species such as the dog are prone to occur when intubation is performed in man under such circumstances.

Cough and straining in response to irritation of the trachea by an endotracheal tube or catheter may add to the circulatory changes mentioned. The circulatory consequences of the Valsalva maneuver may be reproduced. Closure of the bronchi and a prolonged expiratory effort during cough can lead to hypotension and circulatory collapse through interference with the return

of venous blood to the thorax and right atrium. The type of heart disease and the anesthetic agent employed may enhance or minimize the effect of the Valsalva maneuver. Thus, if there is a high central venous pressure, as in mitral stenosis or constrictive pericarditis, the effect of increased intrathoracic pressure on venous return to the heart will be minimized.¹⁶ Similarly if an agent such as cyclopropane is used, which is associated with the development of a high central venous pressure in deep anesthesia, the effect of the Valsalva maneuver is not apt to be as great as with other agents. The patient with a poor cardiac output or the patient with diminished coronary arterial blood flow is apt to die suddenly when the Valsalva maneuver is exerted coincident with the circulatory depressant effects of anesthetic drugs. We have seen patients with heart disease die when the trachea was suctioned to remove secretions in the treatment of atelectasis. Similarly we have seen patients with aortic stenosis and aortic insufficiency die during induction of anesthesia when uncontrolled cough ensued.

The internist must have observed events such as those related here to realize that often it is the anesthetic management rather than the choice of anesthetic agent that leads to circulatory difficulties and sometimes death.

A good rule for medical consultant, surgeon, and anesthetist to observe is that the anesthetic procedure ought never to be more hazardous or complicated than the proposed operation. Local anesthesia is a simple technique. Most of the undesirable pharmacologic and technical accompaniments of general anesthesia are avoided with this method. In using local anesthesia, however, one must be sure that apprehension during the course of operation with a consequent endogenous release of sympathomimetic amines, does not increase the work of a diseased heart. A disproportion between the demands of the myocardium for oxygen and the available coronary arterial blood flow may lead to ischemia or infarction. Likewise, the possible hy-

potensive and myocardial depressant effects of local anesthetic agents should be anticipated. Rapid absorption from the injection site with the development of high blood concentrations gives rise to these quinidine-like effects. These remarks should not negate the value of local anesthesia. Proper preanesthetic preparation, use of minimal quantities of anesthetic, and good technic will eliminate these sequelae.

The versatile anesthetist often elects spinal as a type of local anesthesia for surgical procedures in the cardiac patient. This choice sometimes confounds the medical consultant who is aware of the fact that arterial hypotension is common with this method. Yet spinal is probably the least stressful anesthetic of all from the standpoint of administration. The respiratory, metabolic, and technical disadvantages of general anesthesia are lacking. Muscle relaxation is excellent during operation and hypotension can be controlled by the prophylactic administration of pressor amines. An important consideration in this instance of hypotension is the lesser cardiac work required against a diminished peripheral circulatory resistance. The need for coronary circulation is not so great and the hypotension is less hazardous to the myocardium.

SURGICAL PROCEDURE

Compounding these anesthetic problems already mentioned is the surgical operation, which in its mere technical aspects poses hazards for the patient with heart disease. We have already mentioned the role that the position of the patient on the operating table might play in the production of hypotension or deficient pulmonary ventilation. Sudden blood loss with the production of hypotension need be mentioned only in passing. Certain surgical manipulations within the thorax or abdomen may produce arterial hypotension, changes in heart rate and rhythm. The best known of these is the abdominal traction reflex that gives rise to arterial hypotension. This reflex has been variously ascribed to traction on the mesen-

tery, to stimulation of the celiac plexus, or to interference with the return of venous blood to the heart by the placement of abdominal packs. Recently it has been shown that mechanical stimulation, particularly to the parietal peritoneum of the upper abdomen, may cause a sudden fall in blood pressure of considerable magnitude.¹⁷ The pathways of this reflex have not yet been mapped out but the adequate stimulus has been assumed to be a deformation of the peritoneum with stimulation of Pacinian corpuscles. In association with hypotension thus produced bradycardia is a frequent complication. It is for this reason that the vagus has been implicated in the reflex arc. In order to explain the rapidity of development of hypotension it has been postulated that the vagus exerts an effect on ventricular myocardial contraction despite anatomic evidence to the contrary. That this reflex is not entirely benign has been shown by the postoperative discovery of silent myocardial infarction in patients with these circulatory changes.¹⁸

SUMMARY

Anesthesia for the patient with heart disease has become increasingly safer with the passage of years due to a better knowledge of the physiology of heart disease and of the pharmacologic action of anesthetic agents themselves. There are few statistics to support the clinical impression that patients with cardiac disease tolerate anesthesia and surgery well but reports are not lacking. The difficulty in gathering statistics lies in an inability to compare results in comparable groups of patients. Anesthesia is but a small part of the total operative experience. The patient with serious heart disease usually undergoes a relatively long period of preoperative preparation. When ready, he is given preanesthetic medication and is subjected to the administration of an anesthetic. The surgical operation is superimposed on these preliminary events. Subsequently, convalescence with its many physiologic adjustments completes the surgical experience.

Anesthetic problems may originate in any of the aforementioned phases of the operative experience. These problems have been briefly reviewed. The most important factor in minimizing the problems of anesthesia itself is the skill and knowledge with which the anesthetic agents are chosen and administered rather than the actual pharmacologic and physiologic effects of the agents themselves. On a background of thorough medical preparation safe anesthesia for the patient with heart disease consists of the careful selection of preanesthetic medication, flawless technique, and use of minimal quantities of anesthetic agents and adjuncts. Despite the attainment of these goals, circulatory and respiratory problems will be encountered. These may be related to the heart disease itself, to medical preparation, pharmacologic side effects, and to a multitude of undesirable respiratory and circulatory reflexes. The latter in turn reside in anesthetic and surgical manipulation. Knowledge of these factors enables the internist to understand the problems of anesthesia and to prepare the patient for the operative experience.

REFERENCES

1. VANDAM, L. D., AND BURNAP, T. K.: Problems in anesthesia for operations on the heart, *New England J. Med.* **255**: 110, 1956.
2. MOORE, F. D.: Bodily changes in surgical convalescence. I. The normal sequence—observations and interpretations. *Ann. Surg.* **137**: 289, 1953.
3. LOWN, B., AND LEVINE, S. A.: *Current Concepts in Digitalis Therapy*. Boston, Little Brown & Co., 1954.
4. MARGOLIN, E. G., LEVINE, H. D., AND MERRILL, J. P.: Cardiac arrhythmias associated with provera-trine. *Am. Heart J.* **52**: 257, 1956.
5. DRIPPS, R. D., VANDAM, L. D., PIERCE, E. C., OECH, S. R., AND LURIE, A. A.: The use of chlorpromazine in anesthesia and surgery. *Ann. Surg.* **142**: 774, 1955.
6. WILSON, G. M., EDELMAN, I. S., BROOKS, L., MYRDEN, J. A., HARKEN, D. E., AND MOORE, F. D.: Metabolic changes associated with mitral valvuloplasty. *Circulation* **9**: 199, 1954.
7. DREW, J. H., DRIPPS, R. D., AND COMROE, J. H.: Clinical studies on morphine. II. The effect of morphine upon the circulation of man and upon the circulatory and respiratory responses to tilting. *Anesthesiology* **7**: 44, 1946.
8. KALSER, M. H., FRYE, C. W., AND GORDON, A. S.: Postural hypotension induced by atropine. *Circulation* **10**: 413, 1954.
9. HARVEY, W. P., BERKMAN, F., AND LEONARD, J.: Caution against the use of meperidine in patients with heart disease particularly auricular flutter. *Am. Heart J.* **49**: 758, 1955.
10. PRICE, H. L., AND HELRICH, M.: The effect of cyclopropane, di-ethyl ether, nitrous oxide, thiopental and hydrogen ion concentration on the myocardial function of the dog heart-lung preparation. *J. Pharmacol. & Exper. Therap.* **115**: 206, 1955.
11. BREWSTER, W. R., JR., ISAACS, J. P., AND WAINO-ANDERSEN, A. T.: Depressant effect of ether on myocardium of the dog and its modification by reflex release of epinephrine and norepinephrine. *Am. J. Physiol.* **175**: 399, 1953.
12. ARTUSIO, J. F.: A detailed description of the first stage of ether anesthesia in man. *J. Pharmacol. & Exper. Therap.* **111**: 343, 1954.
13. LYNN, R. B., AND SHACKMAN, R.: The peripheral circulation during general anesthesia and surgery. *Brit. M. J.* **2**: 333, 1951.
14. VANDAM, L. D., AND McLEMORE, G. A., JR.: Circulatory arrest in patients with complete heart block during anesthesia and surgery. *Ann. Int. Med.* **47**: 518, 1957.
15. KING, B. D., HARRIS, L. C., GREIFENSTEIN, F. E., ELDER, J. D., JR., AND DRIPPS, R. D.: Reflex circulatory responses to direct laryngoscopy and tracheal intubation performed during general anesthesia. *Anesthesiology* **12**: 556, 1951.
16. PRICE, H. L., AND CONNER, E. H.: Certain aspects of the hemodynamic response to the Valsalva maneuver. *J. Appl. Physiol.* **5**: 449, 1953.
17. ROCCO, A. G., AND VANDAM, L. D.: Circulatory responses to intra-abdominal manipulation during surgery. *J.A.M.A.* **164**: 14, 1957.
18. MENDELSON, D., JR., AND MONHEIT, R.: Electrocardiographic and blood pressure changes during and after biliary tract surgery. *New England J. Med.* **254**: 307, 1956.

ABSTRACTS

Editor: STANFORD WESSLER, M.D.

Abstracters

DOMINGO M. AVIADO, JR., M.D., Philadelphia
GEORGE B. BROTHERS, M.D., Nashville
MASSIMO CALABRESI, M.D., West Haven
CHARLES D. ENSELBERG, M.D., New York
JOHN C. HARVEY, M.D., Baltimore
J. RODERICK KITCHELL, M.D., Philadelphia
SEYMOUR KRAUSE, M.D., Pittsburgh
GEORGE S. KURLAND, M.D., Boston
EUGENE LEPESCHKIN, M.D., Burlington
MORTON H. MAXWELL, M.D., Los Angeles

MORTON J. OPPENHEIMER, M.D., Philadelphia
ALFRED PICK, M.D., Chicago
SEYMOUR H. RINZLER, M.D., New York
WAYNE R. ROGERS, M.D., Portland
ELLIOT L. SAGALL, M.D., Boston
CHARLES R. SHUMAN, M.D., Philadelphia
LOUIS A. SOLOFF, M.D., Philadelphia
S. O. WAIFE, M.D., Indianapolis
MARTIN H. WENDKOS, M.D., Philadelphia

CONGENITAL ANOMALIES

Cottier, H., and Tobler, W.: Cor Triatriatum Sinister with Stenosis in the Anomalous Septum. *Cardiologia* 30: 46, 1957.

Cor triatriatum sinister is an extremely rare congenital malformation of the heart consisting in an anomalous accessory septum in the left atrium with 1 or more openings permitting blood flow in the normal direction. The authors collected 12 such cases from the literature and present clinical, roentgenologic, and autopsy findings in a personal observation of a 4-month-old infant in whom right heart failure, congestion, induration of the lungs, and early death were attributable to the smallness of the septal communication between the 2 portions of the divided atrium acting as an obstruction to the flow to the left ventricle. The mitral valve was entirely normal. The embryology and pathogenesis of this unusual malformation are discussed. From the practical standpoint it is of interest, since it may be amenable to surgical correction.

PICK

Sen Gupta, S. N., and Ghosh, J. C.: Case of Reverse Coarctation Syndrome. An Aortic Arch Syndrome. *Brit. M. J.* 1: 137 (Jan. 19), 1957.

A 51-year-old man demonstrated sunken cheeks and eyes, bilateral lenticular opacities, and absent pulses in the radial, brachial, axillary, subclavian, carotid, and temporal arteries bilaterally. The pulsation of the aortic arch was forceful in the suprasternal notch and the pulsations of the abdominal aorta and arteries of the legs

were normal. The blood pressure in the legs was 220/75 mm. Hg. There was no history of chest trauma. The blood Wassermann reaction was negative. The patient died of bronchopneumonia.

Autopsy, confined to the aorta and adjacent right lung, revealed in the aorta numerous calcific intimal plaques. There was "a big greyish-white friable clot about 5 × 1.5 cm." attached to the upper wall of the aortic arch and occluding the mouths of all 3 major branches. Less than about two-thirds of the diameter of the arch was patent. The arch was not dilated. Histologically there was no medial or adventitial change to suggest syphilis. The authors suggest that this is an instance of full-blown aortic syndrome on the basis of atherosclerosis which, as a primary cause, has been thought to be unusual.

McKUSICK

Campbell, M.: Cerebral Abscess in Cyanotic Congenital Heart-disease. *Lancet* 1: 111 (Jan. 19), 1957.

Fifteen patients, all with right-to-left shunts, most with tetralogy of Fallot, developed brain abscesses. Campbell considers cerebrovascular thrombosis with secondary infection as the most likely mechanism.

McKUSICK

Coulshed, N., and Littler, T. R.: Atrial Septal Defect in the Aged. *Brit. M. J.* 1: 74 (Jan. 12), 1957.

The authors describe 5 patients, ages 79, 68, 67, 58, and 59 with atrial septal defect. The re-

ports illustrate that this defect is consistent with long life and is likely to be misdiagnosed as coronary artery disease, rheumatic heart disease with mitral stenosis, chronic cor pulmonale, etc., in this age group. In 1 patient an alleged pericardial friction rub persisted for 5 years. It had a superficial quality and became louder with pressure on the stethoscope. Although it may have been incorrectly interpreted to represent systolic and diastolic murmurs, the authors suggest that it was "produced by the enormously dilated pulmonary artery coming into contact with the anterior chest wall, its vigorous pulsation producing the friction sound."

McKusick

Richman, S. M., Thomas, W. A., and Konikov, N.: Survival of Rats with Induced Congenital Cardiovascular Anomalies. The Use of Trypan Blue as a Practical Experimental Approach to Production of Congenital Cardiovascular Anomalies in Rats Capable of Long Postnatal Survival. Arch. Path. 63: 43 (Jan.), 1957.

A practical method is presented for the production of congenital cardiovascular anomalies in rats that are capable of surviving for at least 1 month after birth. Thirty pregnant rats were injected subcutaneously with trypan blue 8½ days after insemination. These rats gave birth to 216 young rats, and 191 of these survived for 22 days or more after birth. Fifty of these 191 were killed at 22 to 33 days of age. Of these 50 rats, 26 had major cardiovascular anomalies. Interventricular septal defects were present in 17 and represented the most common single malformation. None of the animals showed evidence of congestive heart failure in spite of the presence of major anomalies. It was therefore impossible to distinguish between the "control" group and the group with anomalies until the final autopsies were performed.

MAXWELL

Chiechi, M. A.: Incomplete Transposition of the Great Vessels with Biventricular Origin of the Pulmonary Artery (Taussig-Bing Complex). Report of Four Cases and Review of the Literature. Am. J. Med. 22: 234 (Feb.), 1957.

The Taussig-Bing Complex consists of a transposed aorta, a large pulmonary artery that arises primarily from the right ventricle and partially overrides the ventricular septum, a high ventricular septal defect, and right ventricular hypertrophy. Four cases are reported and the literature is reviewed. Cyanosis and intense dyspnea, clubbing, stunted growth and progressive cardiac decompensation were present. X-ray revealed increased pulmonary circulation with hy-

perpulsatile hilar vessels, and the electrocardiogram showed right ventricular hypertrophy. The differential diagnosis was difficult and included all the congenital heart anomalies with cyanosis and increased pulmonary blood flow. Angiocardiography may be helpful. Possible surgical approaches were outlined.

KURLAND

CORONARY ARTERY DISEASE

Honey, G. E., and Truelove, S. C.: Prognostic Factors in Myocardial Infarction. Lancet 1: 1209 (June 15), 1957.

The long-term prognosis of the 348 survivors of 543 cases of acute myocardial infarction was studied. About 14 per cent of the survivors died during the remainder of the first year, 10 per cent the second year, and about 5 per cent annually thereafter. Patients displaying 1 of the following factors constituted a bad-risk group and had 4 times the chance of dying during the first year as a group without them: congestive heart failure, cardiac arrhythmia, gross cardiac enlargement, previous attack of myocardial infarction. Among the good-risk group recurrent infarction was the chief cause of death within 5 years of the acute attack. The incidence was high among patients under 60 years of age. Patients of the good-risk group over 60 years of age had a life expectation the same as that of other people of their age and sex.

KURLAND

Saphire, E. J.: Arterial Oxygen Saturation in Myocardial Infarction. New York State J. Med. 57: 1614 (May 1), 1957.

Four of 16 patients with myocardial infarction had arterial anoxemia with saturations ranging from 84.7 to 93.3 per cent. Three patients had low normal saturations ranging from 94.5 to 95.3 per cent. Arterial hypotension and pulmonary edema appeared to be the most significant factors associated with the development of anoxemia. As factors leading to the development of anoxemia, the age of the patient, the occurrence of previous myocardial infarction, and the location and size of the infarction were not significant. Moderate degrees of congestive heart failure or cardiac arrhythmias were not encountered in this limited series. Oxygen therapy by tent restored the arterial oxygen saturation of the moderately anoxic patients to normal levels but did not appear to be adequate in 2 more severely anoxic patients. It had no measurable effect in 1 patient whose saturation was already within normal levels at the time of infarction. Oxygen tent therapy did not appear to be effective in increasing the

arterial oxygen saturation in patients with normal saturation at the time of infarction.

HARRIS

Eckstein, R. W.: Effect of Exercise and Coronary Artery Narrowing on Coronary Collateral Circulation. *Circulation Research* 5: 230 (May), 1957.

A moderate degree of circumflex arterial constriction is required to induce collateral vascular growth in resting dogs and that collateral development is then proportional to the degree of constriction. The addition of exercise to mild arterial narrowing results in significant collateral anastomoses, and also promotes collateral growth above that due to moderate and severe constriction. It is therefore suggested that during the early stage of coronary disease, exercise may be particularly effective in promoting collateral growth that would not otherwise occur. Since the onset of coronary disease is not clinically recognizable, it would probably be advisable to encourage middle age human beings who are without symptoms to exercise. It is also probable that patients without recent infarcts who have exertional pain due to coronary disease should be placed in a positive program of mild exercise that falls short of producing pain.

AVIADO

Clarke, N. E., Clarke, C. N., and Mosher, R. E.: Treatment of Angina Pectoris with Disodium Ethylene Diamine Tetraacetic Acid. *Am. J. M. Sc.* 232: 654 (Dec.), 1956.

A solution of 5 Gm. of disodium ethylene diamine tetracetic acid (EDTA) in 500 ml. of 5 per cent glucose was administered to 20 patients with coronary artery disease to evaluate the effect of chelation upon bound calcium within the organic atheromatous matrix. A series of 10 to 15 infusions was employed in most instances. Previous observations were cited to demonstrate the ability of EDTA to remove metastatic calcification, especially from the endocardium. The earlier experience indicated that the in vivo action of this compound may persist long after its administration. Fourteen of the 20 patients showed definite electrocardiographic evidence of myocardial damage; in 6 of these, the abnormal tracings reverted to normal patterns. Of the 20 patients there were 19 survivors each of whom obtained marked symptomatic relief. One patient died with what was considered to be a calcium embolus freed from an arterial plaque. The serum stability, measured by determining the surface tension of serum, was restored to normal in the atherosclerotic patients by EDTA, the values being subnormal in the untreated state. Athero-

sclerosis is attributed to a primary change in mucoid ground substance containing highly polar polysaccharides capable of fixing calcium and cholesterol. Removal of calcium by means of chelation may offer a reasonable prospect for success in the treatment of this disorder.

SHUMAN

Mowbray, J. H., and Hamilton, J. D.: The Manner of Death in Coronary Artery Disease. *Canad. M. A. J.* 76: 9 (Jan. 1), 1957.

The coronary arteries of 100 consecutive autopsies were studied by means of a special formalin perfusion and dissection technique that disclosed lesions sufficient to explain death in 22 patients. In all of 10 patients with recent myocardial infarction, corresponding coronary thrombosis was found. In 6 of these recurring coronary thrombosis was noted, suggesting the existence of a thrombotic tendency that might have been counteracted by anticoagulant therapy. Acute coronary insufficiency was considered to have existed in 5 patients showing coronary narrowing, focal myocardial necrosis, in which the terminal event was precipitated by a reduction in cardiac output. Two instances of each of the following conditions were seen: acute coronary thrombosis without infarction, coronary stenosis with sudden death, and coronary stenosis with chronic heart failure. Coronary embolism was present in 1 patient.

ROGERS

Holger-Madsen, T.: Plasma Fibrinogen and Erythrocyte Sedimentation Rate in Myocardial Infarction. *Acta med. scandinav.* 156: 351 (Jan. 15), 1957.

A series of 28 patients with acute myocardial infarction was studied to determine whether measurement of the plasma fibrinogen offered any advantage over measurement of the sedimentation rate in the diagnosis and evaluation of the severity of this disorder. Three patients died before a rise in fibrinogen level was observed. In 5 of the remaining 25 patients there was no significant rise in the fibrinogen level, whereas only 1 of the 25 patients failed to show an increase in sedimentation rate. Abnormal values for both determinations appeared in most patients within the first 3 to 5 days after the onset and maximal values occurred almost simultaneously in most patients at the end of the first week or beginning of the second week. On the average, abnormal values appeared earliest in the patients who were most severely ill. Although there was fairly good agreement, there was no complete parallelism of the highest and lowest values for fibrinogen and the sedimentation rate,

In most patients the plasma fibrinogen level reached a normal value in 5 weeks after the onset, often within the second or third week. On the other hand, the sedimentation rate tended to be elevated longer, frequently until the fifth or sixth week or longer. In only a single patient who was severely ill was the plasma fibrinogen level elevated without a correspondingly increased sedimentation rate. In a few patients there was a discrepancy between the severity of the clinical picture and either the fibrinogen level or the sedimentation rate or both. These determinations were normal in 5 patients with angina decubitus but they were somewhat elevated in 4 patients with congestive heart failure and pulmonary congestion. The plasma fibrinogen determination is believed to offer no advantages over the sedimentation rate in the diagnosis or evaluation of myocardial infarction.

ROSENBAUM

Raab, W.: Progress in the Field of Coronary Disease. *die Medizinische* 1957: 1 (Jan. 5), 1957.

Among the most important achievements of the past 10 years is the recognition of the role of excessive fat consumption and physical inactivity in the genesis of coronary atheromatosis. These factors lead to a high plasma level of lipoproteins of high molecular weight, coupled with metabolic disturbances in the coronary intima that are probably caused by neurohormonal imbalance. Instead of the purely mechanical concept of coronary insufficiency, the role of the antagonism between oxygen-wasting, hypoxia-producing catecholamines and oxygen-preserving acetylcholine is becoming more widely recognized. Long-range treatment of angina pectoris is based on measures, directly or indirectly counteracting the hypoxiating action of the catecholamines (sympathectomy, ganglionic block, adrenal irradiation, antithyroid treatment). Attempts to prevent coronary disease by developing a more effective vagal influence on myocardial oxygen economy through continuous, systematic physical exercise appear justified. In view of the growing mechanization and motorization of our life, the most promising way of furthering such physical training would be a thoroughly organized back-to-walking or bicycling movement.

LEPESCHKIN

Walther, R. J., Starkey, G. W. B., Zervopolus, E., and Gibbons, G. A.: Coronary Arteriovenous Fistula. Clinical and Physiologic Reports on Two Patients, with Review of the Literature. *Am. J. Med.* 22: 213 (Feb.), 1957.

The clinical and physiologic characteristics of 2 cases of coronary arteriovenous fistula are presented and the findings compared to 11 previously reported cases. Such patients have a continuous murmur heard best to the left of the sternum in the pulmonic area or below. The electrocardiogram may be normal or may show left ventricular preponderance, left bundle-branch block, ST-segment or T-wave abnormalities. By x-ray, prominence of the main pulmonary artery, cardiac enlargement, left ventricular prominence, and left atrial enlargement have been seen. Cardiac catheterization indicates a left-to-right shunt of variable size and may reveal the location of the fistula. An apparently good prognosis in the asymptomatic patient suggests that surgery may reasonably be deferred in this group.

KURLAND

Kroop, I. G., and Shackman, N. H.: The C-Reactive Protein Determination as an Index of Myocardial Necrosis in Coronary Artery Disease. *Am. J. Med.* 22: 90 (Jan.), 1957.

The C-reactive protein, an abnormal serum globulin formed in response to infection, necrosis, and neoplasia and so called because it forms a precipitate with C-polysaccharide of pneumococcus, was measured in 100 patients with coronary disease. It was present in 12 to 72 hours after each of 34 cases of transmural myocardial infarction and disappeared after 2 to 5 weeks. Any recurrence indicated a complication. C-reactive protein determination was repeatedly negative in 35 patients with coronary artery disease without myocardial necrosis and in the premonitory phase of coronary occlusion. It was positive where recent necrosis occurred in symptomatic cases of old infarction. C-reactive protein was not found in people with hiatus hernia, cholecystitis, or cholelithiasis. It was concluded that the C-reactive protein determination was a valuable aid in establishing irreversible injury to the myocardium. A positive test after it had previously become negative was helpful in indicating a complication such as phlebothrombosis or recurrent myocardial infarction.

KURLAND

PHYSIOLOGY

Ferguson, D. J., and Berkas, E. M.: Effect of Lung Denervation on Pulmonary Hypertension and Edema. *Circulation Research* 5: 310 (May), 1957.

Under conditions of high pulmonary artery pressure and flow produced in dogs by a controlled systemic artery shunt, pulmonary edema occurred after denervation of the lung at arterial pressures that were tolerated without edema be-

fore denervation. It is suggested that the pulmonary nerves serve chiefly to protect capillaries from excessive arterial pressure but the exact details of such a reflex mechanism (sensory receptor, efferent vagus, or sympathetic) are not known.

AVIADO

Parrish, A. E., Kleh, J., and Fazekas, J. F.: Renal and Cerebral Hemodynamics with Hypotension. *Am. J. Med. Sc.* 233: 35 (Jan.), 1957.

Cerebral and renal hemodynamics were determined simultaneously in subjects with renal and cerebral vascular insufficiency during acute and prolonged reduction of mean arterial pressure by a ganglionic-blocking agent. Anuria and an increased cerebral arteriovenous oxygen difference occurred with an acute reduction in mean arterial blood pressure. With a more prolonged reduction in mean arterial pressure the cerebral vascular resistance and filtration fraction decreased significantly without change in cerebral blood flow or renal plasma flow. These changes indicate usually efficient homeostasis of both the cerebral and renal circulations, accomplished perhaps in these subjects by maximum dilatation of relatively normal vessels and probably at the expense of blood flow in diseased arterioles. Although the vascular responses of brain and kidney to acute and prolonged hypotension induced by Arfonad are similar in many respects, there exists a critical rate of blood flow below which they differ. In severe hypotension there may be renal vasoconstriction whereas the cerebral vessels undergo vasodilatation. The authors conclude that in subjects with vascular disease, renal and cerebral vessels may compensate for significant reductions in blood pressure.

HARRIS

Eddleman, E. E., Jr., Hefner, L., Reeves, T. J., and Harrison, T. R.: Movements and Forces of the Human Heart. I. The Genesis of the Apical Impulses. *Arch. Int. Med.* 99: 401 (March), 1957.

The normal apex impulse may be divided into 2 parts. The first of these, which begins about 0.08 second after the beginning of electric excitation, is believed to be related to recoil as the right ventricle ejects. This portion of the apex beat is associated with sharp outward movement of the right portion of the epigastrium and is delayed in persons with right bundle-branch block but not in those with left. The second portion of the apex beat begins about 0.11 second after the onset of electric excitation and about 0.01 second before the beginning of the carotid upstroke. This portion of the apex thrust is be-

lieved to be of left ventricular origin and, since this second portion of the apex thrust is accompanied by sharp outward movements in the left epigastric region and in the left axilla, it is believed that recoil as the left ventricle ejects is a factor in its production. Various conditions that may cause exaggeration of the apex thrust have been studied. It is concluded that most such conditions (aneurysm of the left ventricle, anginal attacks with ischemia of the apex, and left ventricular hypertrophy) are associated with a disproportion between the strength of the muscles at the base and at the apex of the left ventricle, respectively. The result is an aneurysmal bulge of the apex of the left ventricle due to the more forcible contraction of the stronger muscles at the base.

BERNSTEIN

Kaiser, G. C., Edgecomb, J. H., and Kay, J. H.: Ventricular Fibrillation. An Experimental Study Comparing Various Voltages and Durations of Electric Shock in Defibrillation of the Canine Heart. *J. Thoracic Surg.* 33: 537 (April), 1957.

Because of the absence of agreement as to the optimal voltage and duration of electric shock used for defibrillation, the authors undertook this study. Ventricular fibrillation was induced in 48 dogs, using a standard technique in all. The hearts were allowed to fibrillate for 4 minutes, and were then subjected to cardiac massage for 2 minutes before beginning attempts to defibrillate. Shocks of 130 volts for 0.25 second and 0.10 second were compared with shocks of 230 volts for 0.25 second and 0.10 second. There appeared to be no difference in efficacy. However histologic examinations disclosed a higher incidence of burns in cardiac tissue with 230 volts for 0.25 second.

ENSELBERG

Adams, F. H., and Lind, J.: Physiologic Studies on the Cardiovascular Status of Normal Newborn Infants (With Special Reference to the Ductus Arteriosus). *Pediatrics* 19: 431 (March) 1957.

This is a study of 8 newborn infants upon whom the cardiovascular status was determined by means of cardiac catheterization and determination of cardiac volume done in the immediate postpartum period, 3 to 4 days after birth, and again 2 to 3 weeks after birth. The earliest determination was done 7 hours after birth. Pressures were recorded in the right atrium and ventricle and in the pulmonary artery and occasionally in the left atrium via the foramen ovale. Samples of blood were obtained from each

chamber in which pressure was measured. Cardiac volume was determined. The results of these show that pressure adjustments within the heart after birth take place gradually over a period of many days and not immediately within several minutes postpartum and that the ductus arteriosus remains functionally patent with a large left-to-right shunt for many days after birth. Changes in the cardiac volume are related to the presence and magnitude of the left-to-right shunt through the ductus arteriosus.

HARVEY

Henning, U.: Experimental Studies in Animals on Cardiac Death due to Overexertion by Running in the Drum. *Ztschr. Kreislaufforsch.* 46: 25 (Jan.), 1957.

Twenty rats were forced to run in a drum lined with foam rubber at a velocity of about 1.6 Km. per hour. After 30 to 45 minutes the animals started to stumble, after 60 to 70 minutes they were falling down constantly, and after 90 to 105 minutes they developed slow, very deep respiration and died a few minutes afterwards. The electrocardiogram at the time of slow respiration showed elevation of the S-T segment with pointed upright T wave; terminal S-T segment depression and inversion of the T wave appeared. Death occurred through ventricular fibrillation in 7 animals and cardiac standstill in the others. All animals showed acute congestion in the systemic circulation, dilated lungs and marked dilatation of the right ventricle. Histologic changes were found only in the left ventricle, where the muscle fibers had a looser structure and a more longitudinal course; in 8 animals disseminated loss of staining was found. The cardiac failure was attributed primarily to right ventricular failure due to pulmonary hypertension, followed by left ventricular damage due to decreased coronary flow.

LEPESCHKIN

Finnerty, F. A., Jr., Gillaudeau, R. L., and Fazekas, J. F.: Cardiac and Cerebral Hemodynamics in Drug Induced Postural Collapse. *Circulation Research* 5: 34 (Jan.), 1957.

When signs of cerebral ischemia were induced by the administration of hexamethonium, or by head-up tilting, or by both, it was found that cardiac output was significantly reduced in all patients. Since, at the time of the development of signs of cerebral ischemia the mean arterial blood pressure varied between 34 and 100 mm. Hg, there appeared to be no critical level of arterial pressure at which cerebral ischemia occurred. In contrast to this, a fairly critical level of cerebral blood flow existed for maintenance of conscious-

ness, since this was reduced to an average value of 30.8 ± 4.6 ml./100 Gm. brain/min. The decrease in cerebral vascular resistance accompanying cerebral ischemia was greater than the decrease in peripheral vascular resistance. Such a decrease, however, was not sufficient to compensate for the lack of blood supply delivered to the brain from the heart. Despite a reduction in cardiac output averaging 47 per cent, approximately the same percentage of its output was diverted to the brain during cerebral ischemia. The cause of cerebral ischemia in these experiments resulted from failure of the cardiac output.

AVIADO

Howarth, S., and Sharpey-Schafer, E. P.: Baroreceptor Responses to Acute Rhythm Changes. *Brit. Heart J.* 19: 39 (Jan.), 1957.

Continuous arterial pressures and forearm flows of 7 patients with paroxysmal tachycardia and 17 with congestive failure were recorded to determine the changes that occurred during the onset and offset of the ectopic rhythm. The first sinus beat terminating the arrhythmia had an unchanged mean pressure and an increased pulse pressure. Thereafter the mean and diastolic pressures decreased for 3 or 4 beats. The forearm flow increased 2.4 to 2.9 times that of the ectopic rhythm. These changes indicated vasodilatation. The first ectopic beat produced an immediate and conspicuous decrease in pulse pressure. The mean pressure remained constant or fell slightly after a few beats. Thereafter the mean pressure rose indicating vasoconstriction. Hexamethonium, which apparently blocks the efferent pathway, prevented a change in mean pressure with the onset of a fast ectopic rhythm although the pulse pressure dropped. These results were consistent with a general theory of baroreceptor responses to acute pulse pressure changes.

SOLOFF

van der Tweel, L. H.: Some Physical Aspects of Blood Pressure, Pulse Wave, and Blood Pressure Measurements. *Am. Heart J.* 53: 4 (Jan.), 1957.

The author presents a physical analysis of some of the hydrodynamic quantities involved in the production and maintenance of the blood pressure in arteries, and compares them to electric analogues. For example, a very simplified electric model of the left ventricle, the arterial system, and the periphery would be that of a current source (the heart) that recurrently rapidly charges a condenser (the ejection of blood), which then discharges through a resistance (the periphery). On this basis various formulas relating some of the different factors concerned are

derived. This analogy, however, considers the blood pressure to be static with the same pressure occurring everywhere in the system at the same time. In introducing the dynamic qualities of the system he compares the propagation of the pulse and the transmission of the pressure impulse through the elastic tubing of the arteries to the transmission of an electric impulse through a cable. Further formulas describing the relationships are expressed and corrections suggested for various complications. He also points out the difficulties involved in measuring blood pressure at the end of a catheter and describes a method for "damping" catheter reflections.

SAGALL

PULMONARY DISEASES

Doyle, E., Goodwin, J. F., Harrison, C. V., and Steiner, R. E.: **Pulmonary Vascular Patterns in Pulmonary Hypertension.** *Brit. Heart. J.* 19: 353 (July), 1957.

Persons with mitral stenosis and pulmonary hypertension show radiologically dilatation of the main pulmonary arteries and main branches and narrowing of the small peripheral arteries confined to the lower and middle zones. These findings were confirmed by angiocardiography. Conventional films also frequently showed haziness and Kerley's lines in the lower zones. Patients with congenital heart disease and pulmonary hypertension had dilated main pulmonary and medium sized arteries. The small peripheral arteries were either dilated or constricted evenly throughout all zones with no localized haziness. Patients with congenital heart disease without severe pulmonary hypertension also had enlargement of the main and medium sized arteries. Peripheral arterial constriction was occasionally seen. Postmortem arteriographic and anatomic changes, when present, confirmed the clinical findings. The regional vascular differences in mitral stenosis were attributed to hydrostatic differences. The increased blood flow in congenital heart disease tended to dilate the peripheral vessels and accounted for the less distinctive pattern found in those with hypertension.

SOLOFF

McGuire, J., Scott, R. C., Helm, R. A., Kaplan, S., Gall, E. A., and Biehl, J. P.: **Is There an Entity Primary Pulmonary Hypertension?** *Arch. Int. Med.* 99: 917 (June), 1957.

A review of the literature of primary pulmonary hypertension and the authors' experience with 1 case suggest that such an entity exists, although it may be exceedingly rare. The majority of reported cases of pulmonary hypertension

demonstrated by cardiac catheterization have not had postmortem study. Many cases that have come to autopsy have shown, on histologic examination, widespread occlusive lesions in the pulmonary vascular tree. However, a small number of cases well studied from the clinical and pathologic point of view showed no anatomic explanation for the pulmonary hypertension or its anatomic counterpart, right ventricular hypertrophy. Until further knowledge affords an explanation, such patients may appropriately be regarded as having primary or essential pulmonary hypertension, analogous to systemic hypertension of unknown etiology.

SIMON

Starosta, K., and Blaha, R.: **Aneurysm of the Main Pulmonary Artery.** *Cardiologia* 30: 289 (May), 1957.

The authors report 3 patients in whom the diagnosis of an aneurysm of the main pulmonary artery was made on the basis of angiocardiography and cardiac catheterization. Two were 53-year-old women complaining chiefly of dyspnea and anginal pain and who, at physical examination, had a loud systolic murmur in the second left intercostal space; in 1 a thrill was palpable. The roentgen and angiocardiographic films suggested a saccular aneurysm of the pulmonary artery. The third case was a 39-year-old woman with symptoms and signs of Ayerza's syndrome. In this instance, the shadow of the aneurysm was fusiform. Cardiac catheterization failed to show evidence of any shunt. The pressure within the aneurysm was elevated in the first and third case and normal in the second. The authors discuss the possibilities of distinguishing clinically true aneurysms from simple dilatation of the pulmonary artery and the various etiologic factors involved.

PICK

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Bellet, S., Guzman, S. V., West, J. W., and Aviado, D. M., Jr.: **The Effects of Molar Sodium Lactate on Cardiac Function: An Experimental Study in Dogs.** *Am. J. M. Sc.* 233: 286 (March), 1957.

Molar sodium lactate given intravenously at a rate of 0.5 ml. per Kg. per minute or more caused a fall in arterial blood pressure, increase in coronary blood flow, decrease in force of myocardial contraction, and electrocardiographic changes consistent with hypopotassemia. Intracoronary injections of molar sodium lactate of 0.5 to 1 ml. duplicated these results and accentuated

ated the electrocardiographic changes. At an intravenous infusion rate slower than 0.5 ml. per Kg. per minute the above changes did not occur. Cardiac output, however, increased. The rate of infusion of molar sodium lactate that proved efficacious in the treatment of cardiac arrest and slow ventricular rates was slower than 0.5 ml. per kg. per minute, indicating that in its clinical use, the toxic or untoward effects of molar sodium lactate are not to be anticipated. Molar sodium lactate has multiple actions on the cardiovascular system, reflected by the changes of the various hemodynamic measurements and the numerous mechanisms of action (pH changes, electrolyte shift, and hypertonicity). The metabolic and electrolyte changes in the heart are probably the important factors in the mechanism of its action in the treatment of slow ventricular rates and cardiac arrest. Molar sodium lactate decreases the extracellular potassium level by promoting the shift of extracellular potassium to the intracellular compartment and also partly by expansion of the extracellular space.

HARRIS

Leichsenring, F.: The Diameter of the Ostia of the Renal Arteries in the Normal and Pathological Aorta. Ztschr. Kreislaufforsch. 46: 188 (March), 1957.

Measurements in 1,000 routine autopsies showed that in the absence of atherosclerosis the diameter of the renal artery ostia and that of the aorta uniformly increases with age. In two thirds of the cases there was no difference in the diameter of the right and left ostium; in the remaining cases the right ostium and kidney were usually smaller. The funnel-shaped initial segment of the renal artery was histologically of the elastic type. Atherosclerosis led very often to the development of stenosis at the ostia, especially of the right renal artery, causing a corresponding decrease in weight of the kidneys. Hypertension was not present in cases showing moderate stenosis of 1 ostium, but it was nearly always present when this stenosis was severe.

LEPESCHKIN

Crosley, A. P., Jr., Brown, J. F., Schuster, B., Emanuel, D. A., Tuchman, H., Castillo, C., and Rowe, G. G.: The Effects of Sodium Lactate on Renal Metabolism in Patients with Kidney Disease. J. Lab. & Clin. Med. 49: 429 (March), 1957.

Sixth-molar sodium lactate was administered to 6 patients with renal disease (benign nephrosclerosis, diabetic nephropathy, and chronic glomerulonephritis). The sodium lactate administration resulted in an enhanced renal oxygen

consumption. The latter increase was probably related to the metabolism of sodium lactate by the kidney and was reflected by an increase in renal arteriovenous oxygen difference, since no significant changes occurred in renal blood flow. This response in Q_{O_2} , as well as the increase in $TmPAH$, demonstrates that the diseased kidney is not abnormal in its response to this agent. Since the results and conclusions were the same whether the nitrous oxide or Fick PAH methods were used for the determination of renal blood flow, the data support the use of the former technique as a new means for studies of renal oxygen consumption in man.

MAXWELL

Cort, R. L., and Cort, J. H.: Uterine Electrolytes in Pregnancy and Labour. Lancet 1: 718 (Apr. 6), 1957.

In a small group of patients studied by these investigators prolonged ineffective labor was associated with more severe myometrial potassium depletion than in normal labor. Whether this depletion was the cause or the result of abnormal labor could not be decided, but the authors "rather think that it is both."

McKUSICK

RHEUMATIC FEVER

Bywaters, E. G. L., Isdale, I., and Kempton, J. J.: Schönlein-Henoch Purpura. Evidence for a Group B-Haemolytic Streptococcal Aetiology. Quart. J. Med. 26: 161 (April), 1957.

Because of the close clinical and pathologic similarities between Schönlein-Henoch purpura and rheumatic fever and nephritis, 64 cases of the former were investigated for evidence that infection with group A B-hemolytic streptococcus was the causative factor. Serum anti-streptolysin-O titers were raised in one third of the patients, not significantly more than in a control group of nonrheumatic children. Group A B-hemolytic streptococci were isolated in one quarter of the cases of purpura compared to 44 per cent of patients with acute rheumatic fever and 12 per cent of a nonrheumatic control group.

KURLAND

Figley, M. M., and Bagshaw, M. A.: Angiocardiographic Aspects of Constrictive Pericarditis. Radiology 69: 46 (July), 1957.

Extraluminal soft tissue widths in the region of the right atrium were measured in 30 patients with no clinical evidence of pericardial disease. These measured up to 5 mm. In patients with constrictive pericarditis these measurements varied from 4.5 to 8.5 mm.; in patients with

pericardial effusion from 10 to 15 mm. Accessory angiocardiographic signs were straightening and rigidity of the right atrial border, superior and inferior vena caval dilatation, slowing of the intrathoracic circulation; a right ventricle of normal or small size, and slight left atrial dilatation.

SCHWEDEL

ROENTGENOLOGY

Steinberg, I., and Finby, N.: **The Importance of Angiocardiography for Visualizing the Thoracic Aorta.** *Arch. Surg.* 74: 29 (Jan.), 1957.

The significant advances in surgery of the heart and great vessels over the past few years have made the accurate differential diagnosis of tumors of the mediastinum and aneurysms of the aorta a matter of great practical importance. Angiocardiography, when carefully performed, regularly results in opacification of the aorta and provides valuable diagnostic information. The technique of the procedure is described and illustrative cases are presented, which clearly demonstrate its value in diagnosis. Some causes for occasional failure of adequate aortic opacification to occur and some advantages of angiocardiography are discussed.

BROTHERS

Lyons, H. A., Minnis, J., and Griffin, E.: **The Angiocardiographic Demonstration of Superior Venal Caval Constriction in Constrictive Pericarditis.** *J. Thoracic Surg.* 33: 305 (March), 1957.

Although it is recognized that superior vena caval constriction may be present in constrictive pericarditis it has not previously been demonstrated prior to operation. The authors describe a case of constrictive pericarditis in which angiocardiography clearly demonstrated a sharp constriction of the superior vena cava just at its entrance into the right atrium. At operation a band of fibrous tissue was found at this site, and this was removed in addition to performing a widespread pericardiectomy. This experience emphasizes the usefulness of preoperative angiocardiography in cases of constrictive pericarditis.

ENSELBERG

Gullmo, A.: **The Strain Obstruction Syndrome of the Femoral Vein.** *Acta Radiol.* 47: 119 (Feb.), 1957.

The author discusses the anatomic, physiologic, and abnormal patterns of femoral vein opacification when phlebography was enhanced by increasing intraabdominal pressure by straining, as compared to illustrations without such straining. Ap-

parently this method is valuable in demonstrating lesser grades of femoral venous disease such as incompetent valves, varicosities and venous thromboses than those obtained without the use of this maneuver. Seemingly local variations and herniations in the lacuna vasorum are responsible.

SCHWEDEL

Zacks, A.: **Experimental and Clinical Studies in Radiocardiography.** *Am. J. Roentgenol.* 77: 493 (March), 1957.

Radiocardiography is the graphic recording of variations in the flow of blood through the heart and lungs obtained by the use of radioactive tracer substance injected intravenously. Recordings were first made in an artificial system varying flows and capacities in bottles labeled respectively right heart, left heart, lungs. Increased capacity corresponding to increased chamber volume prolonged tracer time. Diminished flow resulted in similar prolongation. Patients with various clinical states were examined by this method of radiocardiography and the results interpreted in terms of volume capacity and regional flows. The graphs correlated well with the presumed diagnoses. In 1 patient normal tracer time helped in differentiating pericardial effusion from cardiac enlargement, which could well have been assumed to be enlarged on a hypertensive basis. Patterns obtained in cor pulmonale, arteriosclerotic and hypertensive heart disease, valvular disorders, and pulmonary edema correlated well with presumed sites of increased chamber capacity or diminished flow.

SCHWEDEL

Arvidsson, H., and Odman, P.: **Angiocardiography in Mitral Disease. Preliminary Report.** *Acta Radiol.* 47: 97 (Feb.), 1957.

The advantage in the use of rapid serial selective angiocardiography in mitral disease is described. Opacified material was injected into the pulmonary artery trunk through an F10 or F12 catheter with the aid of an automatic pressure syringe. Biplane films were taken of the pulmonary artery and its branches, then after a 2 to 3 second pause during which the lungs were inflated to about 20 mm. Hg, serial films were obtained of the pulmonary veins, left atrium, left ventricle, and aorta. The significance of the dilated pulmonary artery trunk and main branches in contrast to narrowed tertiary and smaller branches is presented. Left atrial and pulmonary venous filling and variations in size (volumetric analysis) apparently can be advantageous in differentiating pure or relatively pure

mitral stenosis from significant mitral insufficiency. The authors also suggest that residual left ventricular blood may indicate, not only the presence of mitral insufficiency, but also occult aortic insufficiency and arterial hypertension.

SCHWEDEL

Nordenstrom, B.: Intracardiac Pressure Changes with Rapid Fluid Injection into the Right Heart. *Acta Radiol.* 47: 89 (Febr.), 1957.

Rapid injection of saline and opacifying substance (Urokon 70 per cent) were made through a selectively placed catheter in 10 dogs. A pneumatic pressure syringe was employed with an injection time of 0.3 to 0.5 second. There was only a slight rise in recorded pressure (1 to 2 mm. Hg) when the injection was made into the venae cavae or the right atrium; a larger rise (20 to 30 per cent rise in systolic levels) for 2 to 7 beats was observed after injection into the right ventricle. Presumably the difference between ventricular and atrial (and caval) pressures was due to the possible run off in the atrium, whereas in the ventricle tricuspid valve closure and pulmonary arterial resistances impeded such an effect.

SCHWEDEL

Soloff, L. A., and Zatuchni, J.: The Angiocardiographic Pattern of High Ventricular Septal Defect with Left to Right Shunt. *Am. J. Med. Sc.* 232: 528 (Nov.), 1956.

A patient with left-to-right shunt through a high ventricular septal defect is described to illustrate the pathognomonic angiocardiographic pattern of this anomaly. The pattern consists of a rapid intracardiac circulation time and a rapid right heart time followed by reopacification of the outflow tract of the right ventricle contiguous with an immediately preceding opacified left ventricle. The demonstration of the reopacified right ventricle through such a shunt can only be made if the right atrium is nonopacified and the right ventricle has been cleared of most of the contrast medium when the left ventricle becomes opacified maximally. The cranial portion of the ventricular septum is virtually parallel to the frontal plane, so that the lateral projection is the one of choice for demonstration of the shunt. The angiocardiogram revealed prolongation of opacification of the left ventricle, outflow tract of the right ventricle, pulmonary artery, and aorta. There was disproportionate enlargement of the pulmonary artery and branches. The left atrium and ventricle and right ventricle may be enlarged.

SCHUMAN

VASCULAR DISEASE

Bebin, J. and Currier, R. D.: Cause of Death in Ruptured Intracranial Aneurysms. *Arch. Int. Med.* 99: 771 (May), 1957.

Among thirty-five autopsies in which death was caused by ruptured intracranial aneurysms, 26 originated from the carotid portion of the circle of Willis and 9 from the basilar part. Intracerebral hemorrhage, subdural bleeding, and intraventricular hemorrhage, alone or in combination, were associated with the fatal subarachnoid hemorrhage. The amount of bleeding into these areas and the length of survival bear a close relationship. Death appears to be related to hemorrhage, operation, ischemic infarction, pneumonia, or compression and obstruction of an unruptured aneurysm acting as a tumor mass. Deaths related to hemorrhage from ruptured intracranial aneurysms are thought to result from hemorrhage into areas other than (but usually in addition to) the subarachnoid space. The most common is intracerebral, with or without intraventricular hemorrhage. Bleeding may also be primarily intraventricular or subdural.

BERNSTEIN

Morgan, W. L.: Important Diagnostic Signs of a Leaking Abdominal Aortic Aneurysm. *Arch. Int. Med.* 99: 134 (Jan. 1), 1957.

A 66-year-old man was found to have a ruptured atherosclerotic abdominal aneurysm. The diagnosis of a leaking aneurysm was made only a week before death after 3 weeks of unexplained fever. The fever of 101 to 103 F., the drop in blood hemoglobin and leukocytosis was explained on the basis of slow retroperitoneal hemorrhage. Until this diagnosis was made, many studies, including cultures, and x-rays, failed to determine the cause of fever. However, a later review of films showed evidence of an enlarging retroperitoneal mass. Four days before death surgical exploration revealed the aneurysm. At autopsy there was no evidence for other disease except an atelectatic lung lobe and minimal portal cirrhosis. Fever, leukocytosis, and progressive anemia suggested infection, which was not confirmed by culture or postmortem examination. These signs in a patient with an abdominal aneurysm should alert the physician to the possibility of slow retroperitoneal hemorrhage.

BERNSTEIN

Phelan, J. T., Bernatz, P. E., and DeWeerd, J. H.: Abdominal Aortic Aneurysm Associated with a Horseshoe Kidney: Report of Case. *Proc. Staff Meet., Mayo Clin.* 32: 77 (Feb. 20), 1957.

In a patient with aneurysm of the distal aorta complicated by the presence of a horseshoe kidney it was possible to excise the aneurysm and to repair the aorta by insertion of an arterial homograft without dividing the isthmus of the horseshoe kidney. Some of the technical problems that might be anticipated are briefly reviewed, along with some of the surgical procedures that could be utilized in the management of such a case.

SIMON

Kaindl, F. Mannheimer, E., Polsterer, P., and Thurnher, B.: **Etiology of Edema in the Limbs.** *Ztschr. Kreislaufforsch.* 46: 296 (April), 1957.

In persons with edema of the leg after venous thrombosis injection of the lymph vessels with roentgenologic dye showed rarefaction of the valves and increased permeability of the vascular wall with extravasation. This finding is not present after ligation of the femoral vein or the inferior vena cava. Its most probable cause is that thrombophlebitis is usually accompanied by lymphangitis. The injection method is also important in the differentiation between the hypoplastic and the ectatic form of primary lymph vessel disease leading to edema of the leg.

LEPESCHKIN

Valenti, C.: **Limb Edema of Pelvic Etiology in Women. Its Evaluation by Means of Pelvic Venography and a Lymphatic Function Test.** *Am. J. Obst. & Gynec.* 73: 380 (Feb.), 1957.

Local factors responsible for edema include lymphatic blockade or venous obstruction. The clinical differentiation between these 2 conditions was aided by the use of venography and a lymphatic absorption test in a group of patients recently subjected to surgery for uterine carcinoma or with pelvic malignant disease treated by irradiation. Venograms were obtained by means of injection of Neo-iopax in 14 patients. Lymphatic function was determined by measuring the rate of absorption of I^{131} albumin injected into the dorsum of the foot. This procedure was performed in 10 control patients and 29 patients with pelvic carcinoma. The results indicated a high incidence of lymphedema in those patients who had received external irradiation to the pelvis. Lymphadenectomy performed during operation for uterine carcinoma represented an important cause of lymphedema in this group. The important factors in the production of leg edema of pelvic etiology include postoperative obstruction of pelvic veins, creation of an extraperitoneal dead space after lymphadenectomy and radiation therapy to the pelvis.

SHUMAN

Lynn, R. B., and Modlin, M.: **Observations on Prevention and Treatment of Gangrene of the Extremities in 211 Patients.** *Surg. Gynec. & Obst.* 104: 99 (Jan.), 1957.

In 211 patients, gangrene of the extremities was attributed to senile atherosclerosis in 107 (including 2 patients with acute arterial thrombosis), diabetic atherosclerosis in 31, trauma in 17, thromboangiitis obliterans in 12, frostbite in 11, Raynaud's disease in 6, infection in 5, and to other causes in 22. Diabetic atherosclerotic gangrene, as contrasted with that of the senile type, is more common in women; it attacks at an earlier age (averaging 67); it is more likely to be amenable to local amputation, probably because the arterial obstruction tends to be more distally situated; and infection and ulceration are more frequent precursors than intermittent claudication. Gangrene of the upper extremities was most commonly due to Buerger's disease and Raynaud's disease was the second most common cause. Efforts toward gangrene prevention involved mainly the avoidance of physical trauma to the ischemic part and the avoidance of infection and of smoking. Once gangrene occurred, amputation was required, and the indications for each of the 4 main types of lower extremity amputation are described. Concomitant lumbar sympathectomy has been found helpful in some patients having amputations below the knee or distally.

ROGERS

Hunt, A. C., and Leys, D. G.: **Generalized Arterial Calcification of Infancy.** *Brit. M. J.* 1: 385 (Feb. 16), 1957.

Some 40 cases have been described of generalized arterial calcification in infants. Both sexes are affected. Death occurs between the ages of 1 day and 27 months, usually in the first 6 months. For a few hours or at the most a few days before death, there are symptoms in the form of refusal of feedings, painful rapid respiration, abdominal distention, and heart failure. The electrocardiogram is likely to show evidences of acute myocardial infarction. The authors describe a brother and sister, both of whom died of this disease at the age of 4 weeks. The cause of the disease is not known. Microscopically the calcification showed a remarkable predilection for the internal elastic lamina. The minimal lesion was a fine incrustation on each side of the elastic strands.

McKUSICK

Myers, T. T.: **Results and Technique of Stripping Operation for Varicose Veins.** *J. A. M. A.* 163: 87 (Jan. 12), 1957.

The surgical principles for treatment of varicose veins in the lower extremity are outlined. They are based on 2,600 stripping operations performed over a 5-year period, and on 510 secondary operations for persistent or recurrent varicosities. Follow-up studies show that excellent results with a minimum of secondary operations can be achieved by proper preparation of the patient, appropriate choice of anesthetics, and good after-care. The stripping operation is the best method yet devised for the treatment of varicose veins. Properly performed it destroys the venous pattern and collateral veins so that recurrences or persistences are uncommon. Good or excellent results were obtained in 94 per cent of the patients.

KITCHELL

Prior, J. T., Buran, R. T., and Perl, T.: Chronic (Healed) Dissecting Aneurysms. *J. Thoracic Surg.* 33: 213 (Feb.), 1957.

A small proportion of cases of dissection of the aorta are not associated with rapid death, but go on to some degree of healing. The authors present a detailed study of 5 such patients, with survival times from 63 days to several years. The pathologic findings varied from organizing intramural hematomas to double-barreled aortas (secondary endothelialized channels with elastification and subintimal proliferation). The authors stress the value of the chest roentgenogram in establishing the diagnosis in doubtful cases. When intimal calcification is present it becomes possible to estimate the thickness of the aortic wall. Thickness of 3 to 10 mm. is suggestive, and more than 1 cm. is practically diagnostic.

ENSELBERG

Baker, C. G., and Finnegan, T. R. L.: Epilepsy and Mitral Stenosis. *Brit. Heart J.* 19: 159 (April), 1957.

The authors collected 22 patients with fits from a total of about 600 who were seen with mitral disease. In all but 4, the onset of fits occurred under circumstances most commonly associated with embolism. Cardiac disability was already present in all and severe in all but 2; atrial fibrillation was present in 12 and paroxysmal atrial fibrillation in 1; and mitral valvotomy had already been performed in 3. Fifteen of the 16 patients subjected to operation had tight mitral stenosis. The remaining patient, developed Jacksonian epilepsy after operation. Only 1 of these 18 had a family history of epilepsy. It appears, therefore, that cerebral embolism is a common cause of fits. These fits respond to anticonvulsant therapy.

SOLOFF

Straffon, R. A., and Buxton, R. W.: Deep Vein Ligation in the Postphlebotic Extremity. *Surgery* 41: 471 (March), 1957.

This paper reports the follow-up observations (1 to 12 years) of the results obtained in 45 patients with femoral vein ligation, and in a small series, of patients after inferior vena cava, iliac and popliteal vein ligations for treatment of postphlebotic sequelae (pigmentation, edema, pain, or fatigue on exercise or at rest, ulceration, varicosities, and static dermatitis). A brief review of the pathophysiology and of the rationale of deep vein ligation in the postphlebotic extremity is presented. The authors were unable to reproduce the advantageous results reported by other surgeons. Meticulous attention to cleanliness of feet, elevation of legs when sitting, carefully fitted elastic support applied prior to rising, prompt interruption of dilated superficial veins and excision and grafting of ulcers that fail to respond to conservative measures gave results more favorable than those obtained with the addition of deep vein ligation. The superiority of deep vein ligation over more conservative symptomatic and supportive measures was not apparent in this group of patients.

BROTHERS

Schoenmackers, J., and Vieten, H.: Blood Vessels of the Liver and Esophagus in Liver Disease with Portal Hypertension. *Arch. Kreislaufforsch.* 25: 222 (Jan.), 1957.

Esophageal varices have probably only a minor role as portacaval anastomoses, as they are seldom filled in angiography; paraesophageal veins, which can scarcely be differentiated from submucous veins in the roentgenogram, have a better connection to the caval circulation. The persistence of portal hypertension after operative creation of portacaval fistulas or in the presence of numerous wide portacaval anastomoses, demonstrated by postmortem angiography, can be explained best by an active hepatic vasoconstriction, analogous to that responsible for systemic hypertension in renal ischemia.

LEPESCHKIN

Walker, R. M.: Portacaval Anastomosis. *Lancet* 1: 57 (Jan. 12), 1957.

In the hands of the author an end-to-side portacaval anastomosis proved most effective in preventing the bleeding of esophageal varices. There were only 3 deaths in 56 cases. The most serious drawback to the operation is the encephalopathy that accompanies large shunts.

McKUSICK

Paterson, M. W.: Ocular Changes in the Pulseless Disease (Takayasu's Disease: The Aortic Arch Syndrome). *Scottish M. J.* 2: 57 (Feb.), 1957.

A 25-year-old woman with the aortic arch syndrome probably on the basis of "young female arteritis" is described. The author emphasizes hypersensitivity of the carotid body and elevated erythrocyte sedimentation rate. The characteristic changes in the eye include granularity of the blood column in the retinal vessels, the progressive formation of arteriovenous anastomoses around the optic disk, and cataract. In the case described, pronounced eye changes developed in the course of 7 months.

McKUSICK

Valaitis, J., Pilz, C. G., and Montgomery, M. M.: Aortitis with Aortic Valve Insufficiency in Rheumatoid Arthritis. *Arch. Path.* 63: 207 (March), 1957.

An unusual type of aortitis with aortic valvular insufficiency occurring in a 38-year-old man with rheumatoid spondylitis is presented. The dilated root of the aorta showed several small aneurysmal outpouchings and marked transverse "tree bark"-like wrinkling of the intimal lining. The rolled aortic leaflets were inverted, and the aortic ring was also dilated. The microscopic findings were those of necrosis of tissue with focal fragmentation of the elastica, preservation of the reticulum, and cellular infiltration. These findings are interpreted as representing a modification of the necrobiotic lesions of rheumatoid arthritis. Histologically, they can be differentiated from the lesions of syphilis and those of rheumatic fever. The described deformities of the aorta and aortic valve, the authors believe, are caused by fibrosis of necrobiotic rheumatoid lesions.

MAXWELL

Blair, J. R., Schatzki, R., and Orr, K. D.: Sequelae to Cold Injury in One Hundred Patients. *J.A.M.A.* 163: 1203 (Apr. 6), 1957.

A follow-up study was carried out in this representative portion of frostbite victims of the Korean war. The original injury involved both feet in 68, 1 foot in 21, the hands in 3, and the hands and feet in 8; tissue loss occurred in 88. Four years after injury, 91 men were employed gainfully although 56 of these were handicapped by sequelae of the injury. Most of them had persistent symptoms including cold feet, pain, numbness, abnormal color, or excessive sweating although the severity did not correlate well with the physical findings. The latter consisted of tissue loss, scars, thickened

ridged nails, erythrocyanosis (or depigmentation in Negroes), hyperhidrosis, and stiff joints. Roentgenographic changes consisted of early transient osteoporosis, mutilation of terminal phalanges, cyst-like defects of the bone near joint surfaces of fingers and toes, early transient periosteal new bone formation, and growth disturbances in patients having open epiphyses.

ROGERS

Lord, J. W., Jr.: Clinical Behavior and Operative Management of Popliteal Aneurysms. *J. A. M. A.* 163: 1102 (March 30), 1957.

Popliteal aneurysm is an uncommon but serious disorder that can be diagnosed readily by physical examination. It is seen mainly in elderly males and usually leads to one or more of these complications: neuralgia distally, popliteal venous compression or thrombosis with leg edema, aneurysmal thrombosis with or without embolism or gangrene, and rupture. Therefore, as soon as the aneurysm is diagnosed it should be treated surgically—by Matas' endoaneurysmorrhaphy if the foot pulses are absent or if the patient is a poor surgical risk, otherwise by excision and grafting. Lumbar sympathectomy is frequently helpful as an adjunct to surgery. The results of these surgical procedures in the elective stage are generally excellent.

ROGERS

Pedowitz, P., and Perell, A.: Aneurysms Complicated by Pregnancy. Part II. Aneurysms of the Cerebral Vessels. *Am. J. Obst. & Gynec.* 73: 736 (April), 1957.

Subarachnoid hemorrhage is described as the most common cerebrovascular accident associated with pregnancy. This condition is frequently secondary to rupture of a cerebral aneurysm for which definite surgical treatment is possible. The clinical and pathologic features of 79 cases of probable or proved cerebral aneurysms, including 2 cases presented by authors, are discussed. The most common location of intracranial aneurysms is at the angle of bifurcation of the vessels of the circle of Willis or in the proximal parts of its branches; the next most common site is at the bifurcation of the internal carotid artery. The aneurysms are regarded as congenital in origin. With rupture of an intracranial aneurysm the symptoms of severe headache and vomiting together with neurologic abnormalities, convulsions, progressing to coma simulate the manifestations of eclampsia. The time of rupture in relation to gestation was the third trimester in 28 patients and during or within 24 hours postpartum in 19 patients. The diagnosis was established by spinal tap and by cerebral angi-

ography. Eleven patients were treated by surgical means, 6 during the course of pregnancy. There were no maternal or fetal deaths in this small group while the over-all maternal death rate was 46 per cent. Concerning rupture of the aneurysm, the mechanism appears to lie in the hemodynamic changes associated with pregnancy rather than in the stress of labor. No conclusions could be reached concerning the ideal method of delivery for these patients. Future childbearing in non-surgically treated cases must be considered individually for each patient.

SHUMAN

Pedowitz, P., and Perell, A.: Aneurysms Complicated by Pregnancy. Part 1. Aneurysms of the Aorta and Its Major Branches. *Am. J. Obst. & Gynec.* 73: 720 (April), 1957.

Aneurysm of the aorta and major branches of the abdominal aorta are serious complications of pregnancy because of the danger of rupture occurring during the gravid state. Two patients with aneurysm of the aorta associated with pregnancy are reported with an analysis of 29 cases of fusiform or saccular aortic aneurysm, 48 of dissecting aortic aneurysms, 35 of splenic, 10 of renal, and 5 of iliac arteries presented from the literature. The important etiologic factors in the formation of aneurysms found in the pregnant patient were anomalies of the aorta and syphilis. Hypertension was regarded as an important precipitating factor influencing the formation of dissecting aneurysms in a diseased aorta with medical necrosis.

Rupture of the aneurysm was rare in the first trimester and reached the peak incidence during the third trimester at the time of the physiologic increase in cardiac output and blood volume. The stress of labor did not appear as an important precipitant of rupture. The clinical features of ruptured aneurysm of branches of the abdominal aorta are indistinguishable from other types of acute abdominal catastrophe. Many obstetric complications may simulate this condition and are more frequently encountered. Surgical correction of sacculated or fusiform aneurysm or of coarctation of the aorta offers the best hope of decreasing maternal mortality associated with rupture of the aorta.

SHUMAN

Tyler, L. T., and Kaplan, I. W.: Paradoxical Gangrene following Lumbar Sympathectomy. *South. M. J.* 50: 63 (Jan.), 1957.

Three cases are described of gangrene occurring almost immediately after lumbar sympathectomy for arteriosclerotic peripheral vascular disease. The authors suggest that one group

of etiologic factors may be traction placed on the sympathetic chain during dissection at lumbar sympathectomy. The authors add the simple procedure of injection of the sympathetic chain and ganglia with 1 per cent Novocain. It is believed that the chain and ganglia are temporarily anesthetized and not sensitive to the stimulation caused by traction and dissection. They suggest that this procedure may prevent the precipitation of gangrene in those patients with poor circulation.

WAIFE

Steinberg, I.: Diagnosis of Arteriosclerotic Aneurysms of the Thoracic Aorta: Report of Six Cases. *Ann. Int. Med.* 46: 218 (Feb.), 1957.

In recent years, more and more aneurysms of the thoracic aorta have been due to arteriosclerosis. This is because the incidence of cardiovascular syphilis is declining while longevity is increasing. Heretofore, discovery of aortic aneurysms was mostly of academic interest; wiring and cellophane wrapping having been of limited success. Newer surgical techniques, especially excision of the aneurysm and replacement with homologous aortic grafts, promise to be a more effective treatment. The early diagnosis of thoracic aortic aneurysm is important, since duration of life, once symptoms begin, is apparently limited. Roentgenography fortunately provides a significant clue by disclosing abnormal mediastinal or hilar shadows. If the vascular nature of the lesions is obscure, contrast visualization of the thoracic aorta by the method of angiocardiology will readily establish the diagnosis. Arteriosclerotic aortic aneurysms may be asymptomatic, but often there is a history of hypertension. When symptoms occur, the situation is ominous. Backache may be due to erosion of the bodies of the dorsal vertebrae by the aneurysm; hoarseness can be caused by recurrent laryngeal nerve paralysis and hemoptysis can be caused by erosion or stenosis of a large pulmonary artery. In a small series of 6 cases diagnosed with the aid of angiocardiology and herein reported, the majority had symptoms due to the aneurysm; of these, 3 were dead within a year. Differentiation from mediastinal tumors may be difficult, if not impossible. It then becomes necessary to perform contrast studies of the cardiovascular system. Angiocardiology can be depended upon to reveal sacular and fusiform aneurysms, as well as dilatation, tortuosity, unfolding, and congenital anomalies of the aorta. The diagnosis of arteriosclerotic aneurysms of the aorta depends upon the presence of a negative history and a negative serologic test for syphilis in the older age groups and the location of

the aneurysm in the arch and descending portions. The absence of severe dilatation and a regular smooth ascending aorta are additional factors that favor the diagnosis of arteriosclerosis. Since the treatment for syphilitic and arteriosclerotic thoracic aneurysms is the same, the etiologic differentiation is often of only academic interest. The decision to perform surgery for arteriosclerotic thoracic aneurysms must take into account the advanced age and the tendency for arteriosclerosis to occur elsewhere. In the heart, there may be coronary thrombosis or insufficiency; in the brain, cerebral thrombosis or hemiplegia; in the abdomen, aortic aneurysm or occlusion; and in the legs, arterial occlusion or insufficiency. Associated diseases like pulmonary fibrosis and emphysema, and kidney or liver disease, also increase the hazards of the surgical treatment. Despite all these, constant vigilance to detect the case suitable for surgery is recommended. Even though not enough time has elapsed to assess the results properly, excision of the aneurysm and replacement by a graft promise to be effective in prolonging life.

WENDKOS

OTHER SUBJECTS

Lillington, G. A., Anderson, M. W., and Brandenburg, R. O.: *The Cardiorespiratory Syndrome of Obesity*. *Dis. Chest*. 32: 1 (July), 1957.

Eight patients were studied who presented a clinical syndrome characterized by extreme obesity, cyanosis, breathing irregularities, congestive heart failure, and a tendency toward excessive lethargy and somnolence. Associated laboratory findings consisted of absolute polycythemia, pulmonary hypertension, arterial hypoxemia, and hypercapnia; compensated respiratory acidosis, alveolar hypoventilation, and abnormalities in the ventilatory tests of pulmonary function. In 4 patients obesity and secondary polycythemia were present without intrinsic pulmonary disease. In 3 patients with primary pulmonary disease, obesity was thought to have played a significant role in the development of hypoxemia and secondary polycythemia. The last patient did not have polycythemia, but pulmonary function tests suggested that he manifested the early stages of ventilatory impairment of obesity. The data suggested that the mechanical effect of obesity in increasing the work of breathing is probably the primary factor in the genesis of the significant alveolar hypoventilation. Appropriate weight loss is accompanied by reversal of these complications even in those patients with primary pulmonary or cardiac disease in whom the obesity acts as an aggravating factor.

MAXWELL

Gilsanz, V., Vergara, A., and Gallego, M.: *A New Method for Determining the Portal Circulation Time. A Spleen-Lung Ether Time*. *Arch. Int. Med.* 99: 428 (March), 1957.

The authors believe that the determination of the spleen-lung ether time is a more reliable, easier, and more precise procedure than splenoportography for the study of the dynamics of the portal circulation. In normal subjects the spleen-lung ether time is approximately 1 or 2 seconds less than the arm-lung ether time. In 5 patients with cirrhosis of the Laennec type, the authors found a marked increase of the spleen-lung circulation time as compared with the arm-lung time. In 2 patients with biliary cirrhosis, the slowing of the portal circulation was not as marked as in the patient with cirrhosis of the Laennec type, but it was, however, markedly increased in a patient with posthepatic cirrhosis, where the difference was very small (3 seconds). In a patient with hemochromatosis the spleen-lung time was somewhat more than double. In a patient with a metastatic neoplasm of the liver the ether time was normal. In one patient with a clinical history of obscure abdominal pains that suggested recurrent pancreatitis because of the finding of a prolonged spleen-lung time (ether), the authors were induced to study the case further, and hepatic biopsy finally proved that it was a case of cirrhosis.

BERNSTEIN

Plotkin, Z.: *The Syndrome of Gastroduodenal Disease Associated with Chronic Cor Pulmonale*. *Dis. Chest* 31: 195 (Feb.), 1957.

The syndrome of gastroduodenal disease associated with pulmonary emphysema and chronic cor pulmonale is described. Of 65 cases of pulmonary emphysema with right heart disease on whom postmortem examinations were performed, 21 revealed peptic ulcer of the stomach and duodenum, and 6 showed hypertrophic gastritis. A like number of clinical cases studied with x-rays of the upper gastrointestinal tract yielded a 30 per cent ratio of peptic ulcers and a high incidence of gastritis. Almost all of these patients, with a few exceptions, did not have the history of pain typical of peptic ulcer. Twenty-five per cent of these patients died from hemorrhage and perforation. The ulcers were frequently located on the lesser curvature of the stomach in the prepyloric area. In the absence of characteristic symptoms, lack of polycythemia in a state of marked hypoxia might occasionally serve as a diagnostic pointer for peptic ulcer or bleeding gastritis in the patient with chronic cor pulmonale.

A discussion of the possible mechanisms by

which chronic cor pulmonale might lead to the development of peptic ulcer is presented. It is recommended that all patients of this group be subjected to x-ray studies and, if necessary, gastroscopic examinations of the gastroduodenal tract. This is the only means of establishing a proper diagnosis and instituting early treatment in order to forestall serious complications.

MAXWELL

Brody, J. I., and Bellet, S.: The Use of Electric Shock Therapy in Patients with Cardiovascular Disease. *Am. J. M. Sc.* 233: 40 (Jan.), 1957.

The over-all incidence of death in electric shock therapy varies from 0.05 to 0.08 per cent. The incidence of death in patients with and without cardiovascular disease receiving electric shock therapy is not significantly different. Three of the 4 patients dying during electric shock therapy at the Philadelphia General Hospital had no cardiovascular disease. Cardiovascular patients may receive electric shock therapy with little more risk than patients showing no evidence of such disease. Hypertensive and arteriosclerotic cardiovascular disease are not contraindications to therapy in the absence of an acute process such as myocardial infarction or thrombophlebitis. Mechanical failure of the heart is the main cause of death with arrhythmias playing a secondary role. Prophylaxis should include muscle relaxants and antiarrhythmic drugs to modify the convulsions. The pathologic physiology of the cardiovascular system during electric shock therapy is discussed.

HARRIS

Marks, A., Cugel, D. W., Cadigan, J. B., and Gaensler, E. A.: Clinical Determination of the Diffusion Capacity of the Lungs. Comparison of Methods in Normal Subjects and Patients with "Alveolar-Capillary Block" Syndrome. *Am. J. Med.* 22: 51 (Jan.), 1957.

This study undertakes to compare in 33 patients with alveolar-capillary block syndrome and 13 normal volunteers, the diffusion capacity of the lungs at rest measured by 3 different methods utilizing carbon monoxide [Dco] (steady state, single breath, fraction removed) and by direct calculation from 2-level alveolar-arterial oxygen "gradients" [D_{O_2}]. The steady state Dco averaged 19.5 ml. per minute per mm. Hg for normal subjects and 7.0 ml. for the patients without overlap. The single breath Dco averaged 30.2 ml. per minute per mm. Hg and 16.8, respectively with some overlap. The fraction removed (Fco) was more than 50 per cent in all but 1 normal and less than 50 per cent in all but 1 patient. The

mean D_{O_2} of 9.1 ml. per minute per mm. Hg compared well with the mean steady state Dco of 7.9. Both Dco methods were more easily performed than the direct D_{O_2} method but only the steady-state technique gave comparable values. The single breath Dco test may prove useful in screening for impaired diffusion but a normal value does not rule out alveolar-capillary block.

KURLAND

Kazmeier, F., Schild, W., Voigt, H. J., and Heymanns, E.: Simple Circulatory Studies in 450 Miners and Their Statistical Analysis. *Arch. Kreislaufforsch.* 25: 178 (Jan.), 1957.

In 250 miners with silicosis the blood pressure was significantly higher than in 200 miners without silicosis; the incidence of right axis deviation in the electrocardiogram was about the same, while abnormal electrocardiograms and ballistocardiograms were significantly more common, especially in the older persons. The total incidence of abnormal circulatory findings, expressed in points, increased with the age and degree of hypertension; it showed no relation to the electrocardiographic findings, but a highly significant correlation with the ballistocardiographic abnormalities.

LEPESCHKIN

Kaindl, F., Mannheimer, E., Polsterer, P., and Thurnher, B.: Delineation and Functional Behavior of the Lymphatic Vessels in Human Extremities. *Ztschr. Kreislaufforsch.* 46: 296 (Feb.), 1957.

Subcutaneous injection of Prontosil or patent blue enables recognition of the superficial lymphatic vessels; migration of the dye for 20 cm. requires an average of 12 minutes. Dissection of the colored lymph vessel and injection of roentgenologic dye directly into it enable visualization of the particular vessel and the corresponding lymph nodes.

LEPESCHKIN

Taylor, G. W., Kinmonth, J. B., Rollinson, E., Rotblat, J. and Francis, G. E.: Lymphatic Circulation Studied with Radioactive Plasma Protein. *Brit. M. J.* 1: 13 (Jan. 19), 1957.

The behavior of I^{131} -labeled plasma protein injected into the subcutaneous tissues of the limbs of human subjects and animals was consistent with removal by the lymphatic route. The removal was slower in patients with lymphedema. In normal subjects it was hastened by exercise. Direct absorption into the blood occurred only in animals after traumatic destruction of the lymphatic pathway.

McKUSICK

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

AHA SCIENTIFIC SESSIONS TO EMPHASIZE PHYSICIANS' USE OF RESEARCH DATA

A program that will place greater emphasis on the practical application by physicians of findings in cardiovascular research is being planned for the 31st Annual Scientific Sessions of the American Heart Association. The Sessions will be held from Friday, October 24 through Sunday, October 26 at the Civic Center, San Francisco. The 1958 Scientific Sessions will commemorate the 10th anniversary of the American Heart Association as a national voluntary health agency.

Tentative plans include an all-day program on clinical orientation for the practicing physician to be sponsored by the Association's Council on Clinical Cardiology. The session will be aimed at bringing to the practicing physician the results of research which he will find most useful in every-day practice.

Several joint sessions are being planned with the American Society for the Study of Arteriosclerosis which has scheduled its Annual Meeting to coincide with the Heart Association's Scientific Sessions.

Applications for the presentation of papers or for scientific exhibit space at the Sessions may be obtained by writing to F. J. Lewy, M.D., Assistant Medical Director of the American Heart Association. Applications will be processed by the Association's Committee on Scientific Sessions Program. Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field.

Abstracts of papers must be limited to 250 words or less to be submitted on official forms provided by the Association before June 13, 1958. They should contain in summary form the results obtained and the conclusions reached.

All applications for space for scientific and technical exhibits must be filed with the Association through Dr. Lewy not later than June 13, 1958.

AGENCY WILL ARRANGE TRAVEL TO WORLD CARDIOLOGY CONGRESS

Travel arrangements to and from the Third World Congress of Cardiology in Brussels, September 14-21, may be made by writing to the Convoys Travel Service, 1133 Broadway, New York, N. Y. The agency also will supply travel information and make arrangements for tours before the Congress or following it. All other information regarding the Congress may be obtained from Dr. F. Van Dooren, Secretary of the Congress, 80 Rue Mercelis, Brussels, Belgium.

DR. PAUL D. WHITE ISSUES HEART MONTH MESSAGE

Paul Dudley White, M.D., of Boston, in a message marking February as American Heart Month, said that "the partnership of the medical profession and the public, and the strength of voluntary support, are vital for the advancement of scientific research which during the past ten years has scored dramatic achievements in the prevention and treatment of cardiovascular diseases."

Dr. White is serving as Honorary Co-Chairman of the 1958 national Heart Fund campaign. Mrs. Dwight D. Eisenhower is Honorary Chairman of the drive.

"During its first decade as a voluntary health agency, the American Heart Association has forged a great partnership of the medical profession, the scientists and the public to help conquer diseases of the heart and blood vessels, the leading cause of death and disability in our nation today," the President's heart consultant said. "Voluntary

citizen action, from which the Heart Association draws its strength, is a particular characteristic of our democracy. Through the research, education and community service programs of the Heart Association, individual citizens are given an opportunity to take positive action in many practical ways against a disease that so closely affects the lives and happiness of every family."

RENEW SUBSCRIPTIONS THROUGH GRUNE AND STRATTON, INC.

Subscription renewals for *Circulation* and *Circulation Research*, official journals of the American Heart Association, should be made directly through the publisher, Grune and Stratton, Inc., 381 Fourth Avenue, New York 16, N.Y. Subscribers who are either members or non-members of the American Heart Association may renew their subscriptions in this manner.

MEETING IS SCHEDULED ON RHEUMATIC FEVER PROGRAMS

A national meeting on the subject of secondary rheumatic fever prevention programs, with attendance by invitation, will be held on March 9 through March 11, in Chicago. Co-sponsors of the meeting will be the American Heart Association and the U.S. Public Health Service. Discussion will cover organization and administration of rheumatic fever prevention programs; the roles of various organizations interested in the problem; methods of obtaining acceptance of the program; case-finding, plan of the case-registry and other follow-up practices; research aspects; and methods of financing and obtaining staff.

BOOK ON RHEUMATIC FEVER BROUGHT UP TO DATE

A completely revised edition of the book "Epidemiology of Rheumatic Fever" by John R. Paul, M.D., Professor of Preventive Medicine at Yale University School of Medicine, has been prepared with the assistance of an ad hoc Advisory Committee of the Ameri-

AMERICAN HEART ASSOCIATION

can Heart Association's Council on Rheumatic Fever and Congenital Heart Disease. Completely rewritten in the light of recent knowledge on the spread and causes of rheumatic fever, the 187-page volume contains information of particular value to pediatricians, health officers and rheumatic fever committees. It is available through local Heart Associations or the national AHA office at \$5.00 a copy.

ENTRIES FOR BLAKESLEE AWARDS NOW BEING ACCEPTED

Entry blanks and instructions for entering the Howard W. Blakeslee Awards competition of the American Heart Association, presented annually for outstanding reporting in the mass media on heart and circulatory diseases, may be obtained from the Association's national office, 44 East 23rd Street, New York 10, N. Y. May 1 is the closing date for submitting entries.

Selections will be made by the Heart Association's Awards Committee from among newspaper and magazine articles, books, radio and television programs and films published or produced between March 1, 1957 and February 28, 1958. The Awards, each of which carries a minimum honorarium of \$500, will be presented next fall.

NEW HEART FILM AVAILABLE

A new motion picture, "Take Three Hearts," which shows how the physician and the Heart Association can help patients suffering from heart and circulatory diseases, has been issued by the American Heart Association. The 16 mm. black and white sound film runs approximately 27 minutes. It is available from local Heart Associations or from the national office of the AHA.

"YOU AND YOUR HEART" BOOK IS REVISED

Particularly suited for distribution by physicians to their patients is the new revised paper-bound edition of "You and Your Heart," published by the New American Li-

brary. Intended for the layman, the volume includes the latest medical findings on diseases of the heart and blood vessels. Written chiefly by H. M. Marvin, M.D., the book contains a foreword by Paul D. White, M.D. and chapters by the late T. Duckett Jones, M.D., Irvine H. Page, M.D., Irving S. Wright, M.D. and Maelyn McCarty, M.D. Copies are available from local Heart Associations or the national AHA office at 50c each.

MEETINGS CALENDAR

- March 9-14: International College of Surgeons, 11th Biennial Congress, Los Angeles. Karl A. Meyer, M.D., 1516 Lake Shore Drive, Chicago 10, Ill.
- March 10-13: Southeastern Surgical Congress, Baltimore. B. T. Beasley, M.D., 45 Edgewood Avenue, S.E., Atlanta 3, Ga.
- March 20-22: Chicago Heart Association, Conference on Pulmonary Circulation, Chicago. Wright Adams, M.D., Department of Medicine, University of Chicago, Chicago, Ill.
- March 24-27: American Academy of General Practice, 10th Annual Scientific Assembly, Dallas. Mac F. Cahal, Volker B'ld. at Brookside, Kansas City 12, Mo.
- March 29-30: American Psychosomatic Society, Cincinnati. Morton F. Reiser, 55 Madison Avenue, New York 22, N. Y.
- April 16-18: American Surgical Association, New York. R. E. Gilchrist, 59 E. Madison Street, Chicago 3, Ill.
- April 24-26: Fifth International Congress of Internal Medicine, Philadelphia. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

April 28-May 2: American College of Physicians, Atlantic City. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

May 1-4: Student American Medical Association, Chicago. Russell F. Staudacher, 510 N. Dearborn, Chicago 10, Ill.

May 4: American Federation for Clinical Research, Atlantic City. William W. Stead, VA Hospital, Minneapolis 17, Minn.

May 5: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Avenue, New York 16, N. Y.

May 6-7: Association of American Physicians, Atlantic City. P. R. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 8-9: American Pediatric Society, Atlantic City. A. C. McGuinness, 2800 Quebec Street N.W., Washington 8, D.C.

June 19-22: American Medical Womens Association, San Francisco. Miss L. T. Majally, 1790 Broadway, New York 19, N. Y.

June 23-27: American Medical Association, San Francisco. George F. Lull, 535 N. Dearborn, Chicago 10, Ill.

ABROAD

April 16-19: International Academy of Legal Medicine and Social Medicine, 50th International Congress, Madrid. Prof. B. Piga, Professor of Legal Medicine, Madrid University, Madrid, Spain.

July 15-21: Medical Women's International Association, London. J. Aitken, M.D., 30A Acacia Road, London, N.W. 8, England.

September 14-21: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Mercelis, Brussels, Belgium.

CONTRIBUTORS TO THIS ISSUE

PIER FAUSTO ANTOGNETTI, M.D.

Assistant Radiologist, Institute of Clinical Medicine of the University, Genoa, Italy.

MARIA AURORA ANTONIO, M.D.

Research Fellow, New York University College of Medicine, New York, N. Y.

ROBERT N. ARMEN, M.D., F.A.C.P.

Director of Professional Services, Veterans Administration Hospital, Brooklyn; Associate Professor of Clinical Medicine, State University of New York, Brooklyn, N. Y.; Formerly, Chief of Medicine, Veterans Administration Hospital, Wilkes-Barre, Pa.

GIULIO BANDIERA, M.D.

Assistant Cardiologist, Institute of Clinical Medicine of the University, Genoa, Italy.

EUGENE BRAUNWALD, M.D.

Clinical Associate, Laboratory of Cardiovascular Physiology, National Heart Institute, Bethesda, Md.

THOMAS K. BURNAP, M.D.

Assistant in Anesthesia, Harvard Medical School; Junior Associate in Surgery, Peter Bent Brigham Hospital, Boston, Mass.

DENTON A. COOLEY, M.D.

Associate Professor of Surgery, Baylor University College of Medicine, Houston, Tex.

W. M. COPENHAVER, PH.D.

Professor of Anatomy, Columbia University College of Physicians and Surgeons, New York, N. Y.

KURT DECRINIS, M.D.

Assistant in Medicine, New York University College of Medicine, New York, N. Y.

CARL L. EBNOTHER, M.D.

Formerly Research Fellow in Cardiology and Resident in Medicine, Veterans Administration Hospital, San Francisco, Calif.

JOHN M. EVANS, M.D.

Associate Professor of Medicine, George Washington University, Washington, D. C.

MELVIN M. FIGLEY, M.D.

Associate Professor of Radiology, University of Michigan Medical School, Department of Radiology, University Hospital, Ann Arbor, Mich.

JOSEPH FISHER, M.D.

Assistant Attending Physician, Lincoln Hospital, New York, N. Y.

CARLOS FORNO, M.D.

Visiting Research Fellow in Medicine assigned to the Vascular Section of the Edward Robinette Foundation, Medical Clinic, Hospital of the University of Pennsylvania, Philadelphia, Pa.; Hospital Arzobispo Loayza, Lima, Peru.

**WILLIAM F. M. FULTON, M.B., CH.B.,
M.R.C.P. (LOND.)**

Lecturer in Materia Medica and Therapeutics, University of Glasgow, and Senior Registrar, Stobhill General Hospital, Glasgow.

DOUGLAS C. HEINER, M.D.

Fellow in Cardiology at Children's Medical Center, Boston, Mass.; Trainee, National Heart Institute, U. S. Public Health Service. Present address, Department of Pediatrics, University of Arkansas, Little Rock, Ark.

EDGAR A. HINES, JR., M.D.

Section of Medicine, Mayo Clinic, Rochester, Minn.

ORVILLE HORWITZ, M.D.

Hospital of the University of Pennsylvania, Assistant Professor of Clinical Medicine, Medical School, University of Pennsylvania, Philadelphia, Pa.

RICHARD D. JUDGE, M.D.

Instructor in Internal Medicine, University of Michigan Medical School, Heart Station, University Hospital; Clinical Investigator, Veterans Administration Hospital, Ann Arbor, Mich.

MILTON KANTOR, M.D.

Assistant Chief of Medical Service, Veterans Administration Hospital, Wilkes-Barre, Pa.

JOHN W. KIRKLIN, M.D., M.S.

Consultant, Section of Surgery, Mayo Clinic; Assistant Professor of Surgery, Mayo Foundation, Graduate School, University of Minnesota, Rochester, Minn.

ARTHUR J. LEWIS, M.D.

Formerly, Research Fellow of the New York Heart Association; Presently, Research Fellow, New York University College of Medicine, New York, N. Y.

DWIGHT C. MCGOON, M.D.

Assistant to the Staff, Section of Surgery, Mayo Clinic, Rochester, Minn.

DAN G. McNAMARA, M.D.

Assistant Professor of Pediatrics, Baylor University College of Medicine, and Director, Cardiac Clinic, Texas Children's Hospital, Houston, Tex.

JOSEPH C. MERRIAM, M.D.

Resident in Pathology, Massachusetts Memorial Hospitals, Boston, Mass.

HUGH MONTGOMERY, M.D.

Hospital of the University of Pennsylvania, Associate Professor of Medicine, Medical School, University of Pennsylvania, Philadelphia, Pa.

ANDREW G. MORROW, M.D., F.A.C.S.

Chief, Clinic of Surgery, National Heart Institute, Bethesda, Md.

ROBERT H. MOSER, M.D., MAJOR, M.C.

Assistant Chief Department of Medicine, Brooke Army Hospital, Fort Sam Houston, Tex.

JEROME P. MURPHY, M.D.

Instructor in Surgery, Creighton University School of Medicine, Attending Surgeon to the Creighton Memorial, St. Josephs Hospital, Omaha, Neb.

ALEXANDER S. NADAS, M.D.

Clinical Professor of Pediatrics, Harvard Medical School; Cardiologist, Children's Medical Center, Boston, Mass.

HAROLD H. ORVIS, M.D.

Formerly, Fellow in Cardiovascular Disease, the Washington Heart Association; Assistant in Medicine, George Washington University; Currently, Resident in Medicine, George Washington University, Washington, D. C.

PETER PACKARD, M.D.

Formerly Resident in Medicine, Veterans Administration Hospital, San Francisco, Calif.

JOHN E. QUINN, M.D.

Formerly Resident in Cardiology, Veterans Administration Hospital, San Francisco, Calif.

KEITH REEMTSMA, M.D.

Resident in Surgery, The Presbyterian Hospital New York, N. Y.

WALTER REDISCH, M.D.

Associate Professor of Clinical Medicine, New York University College of Medicine; Visiting Physician, New York University Research Service, Goldwater Memorial Hospital, New York, N.Y.

RICHARD J. SANDERS, M.D.

Clinical Associate, Clinic of Surgery, National Heart Institute, Bethesda, Md.

ARTHUR SELZER, M.D.

Clinical Professor of Medicine, Stanford University School of Medicine; Attending Physician, Veterans Administration Hospital, San Francisco, Calif.

HERBERT E. SLOAN, JR., M.D.

Associate Professor of Surgery, University of Michigan Medical School, Section of Thoracic Surgery, Department of Surgery, University Hospital, Ann Arbor, Mich.

**GEORGE SMITH, M.B.E., M.D. (St. And.),
F.R.F.P.S.G.**

Senior Lecturer in Surgical Cardiology, University of Glasgow.

REGINALD H. SMITHWICK, M.D.

Professor of Surgery, Boston University School of Medicine; Surgeon-in-Chief, Massachusetts Memorial Hospitals, Boston, Mass.

SHELDON C. SOMMERS, M.D.

Associate Professor of Pathology, Boston University School of Medicine; Pathologist, Massachusetts Memorial Hospitals, Boston, Mass.

J. MURRAY STEELE, M.D.

Professor of Medicine, New York University College of Medicine; Director, New York University Research Service, Goldwater Memorial Hospital, New York, N. Y.

ARTHUR O. STONE, M.D.

Formerly Senior Resident in Medicine, Veterans Administration Hospital, San Francisco, Calif.

SOON KYU SUH, M.D.

Assistant Resident in Medicine, Lincoln Hospital, New York, N. Y.

IRENE G. TAMAGNA, M.D.

Associate in Medicine, George Washington University, Washington, D. C.

FRANCISCO F. TANGCO, M.D.

Formerly, Research Fellow of the New York Heart Association; Presently, Assistant Professor of Medicine, University of the Philippines Medical School, Manila, P. I.

LEROY D. VANDAM, M.D.

Associate Clinical Professor of Anesthesia, Harvard Medical School; Surgeon, Peter Bent Brigham Hospital, Boston, Mass.

KURT N. VON KAULLA, M.D.

Assistant Professor of Medicine, University of Colorado Medical Center, Denver, Colo.

WELDON J. WALKER, M.D., COLONEL, M.C.
Chief of Cardiovascular Service, Brooke Army Hospital, Fort Sam Houston; Assistant Professor of Clinical Medicine (Cardiology), Baylor University Graduate School of Medicine, Houston, Tex.

NELSON J. WEISER, M.D.

Ward physician, Medical Service, Veterans Administration Hospital, Wilkes-Barre, Pa.



*"Since we put him on NEOHYDRIN he's been
able to stay on the job without interruption."*

oral
organomercurial
diuretic

L LAKESIDE

TABLET
NEOHYDRIN[®]
BRAND OF CHLORMERODRIN

24057



CONTENTS

EDITORIAL

CLINICAL ASPECTS OF SOME DISEASES OF THE SMALL ARTERIES AND ARTERIOLES. <i>Edgar A. Hines, Jr.</i>	161
PULMONARY HEART DISEASE: WITH EMPHASIS ON ELECTROCARDIOGRAPHIC DIAGNOSIS. <i>Robert N. Armen, Milton Kanton and Nelson J. Weiser</i>	164
SERUM CHOLESTEROL IN PENTOLINIUM-TREATED ARTERIAL HYPERTENSION. <i>Harold H. Orvis, Irene G. Tamagna and John M. Evans</i>	176
PULMONIC STENOSIS WITH INTACT VENTRICULAR SEPTUM: TREATMENT UTILIZING EXTRACORPOREAL CIRCULATION. <i>Dwight C. McGoon and John W. Kirklin</i>	180
INTRAVENOUS PROTEIN-FREE PYROGEN: A POWERFUL FIBRINOLYTIC AGENT IN MAN. <i>Kurt N. von Kaulla</i>	187
INACCURACY OF WEDGE PRESSURE AS AN INDEX OF PULMONARY CAPILLARY PRESSURE. <i>Jerome P. Murphy</i>	199
SEVERE HEMOPTYSIS DURING PREGNANCY TREATED BY MITRAL COMMISSUROTOMY. <i>William F. M. Fulton and George Smith</i>	204
INTERRELATIONSHIPS OF DRUGS INFLUENCING ARTERIAL PRESSURE IN MAN. <i>Walter Redisch, Francisco F. Tanco, Arthur J. Lewis, Maria Aurora Antonio, Kurt DeCrisis and J. Murray Steele</i>	208
LEFT ATRIAL ELECTROKYMOGRAPHY IN MITRAL INSUFFICIENCY IN MAN: A CORRELATIVE STUDY BY ANGIOCARDIOGRAPHY AND LEFT HEART CATHETERIZATION. <i>Richard D. Judge, Melvin M. Figley and Herbert E. Sloan</i>	213
VENTRICULAR PRECONTRACTING AREA IN THE WOLFF-PARKINSON-WHITE SYNDROME: DEMONSTRATION IN MAN. <i>Giulio Bandiera and Pier Fausto Antognetti</i>	225
PATENT DUCTUS ARTERIOSUS IN ASSOCIATION WITH PULMONIC STENOSIS: A REPORT OF SIX CASES WITH ADDITIONAL NONCARDIAC CONGENITAL ANOMALIES. <i>Douglas C. Heiner and Alexander S. Nadas</i>	232
CLINICOPATHOLOGIC CORRELATIONS OF RENAL BIOPSIES IN HYPERTENSION WITH PYELONEPHRITIS. <i>Joseph C. Merriam, Sheldon C. Sommers and Reginald H. Smithwick</i>	243
CORRECTED TRANSPOSITION OF THE GREAT VESSELS, ATRIOVENTRICULAR HEART BLOCK AND VENTRICULAR SEPTAL DEFECT: A CLINICAL TRIAD. <i>Weldon J. Walker, Denton A. Cooley, Dan G. McNamara and Robert H. Moser</i>	249
RELIABILITY OF ELECTROCARDIOGRAPHIC DIAGNOSIS OF LEFT VENTRICULAR HYPERTROPHY. <i>Arthur Selzer, Carl L. Ebnother, Peter Packard, Arthur O. Stone and John E. Quinn</i>	255
DEXTROCARDIA WITH PULMONARY STENOSIS AND FUNCTIONALLY SINGLE RIGHT VENTRICLE. <i>Joseph Fisher and Soon Kyu Suh</i>	266
ANATOMIC STUDIES OF THE CARDIAC CONDUCTION SYSTEM IN CONGENITAL MALFORMATIONS OF THE HEART. <i>Keith Reemtsma and W. M. Copenhaver</i>	271
INFLUENCE OF AN OSCILLATING BED ON CUTANEOUS TEMPERATURE AND OXYGEN TENSION OF ISCHEMIC TOES. <i>Carlos Forno, Hugh Montgomery and Orville Horwitz</i>	277
THE NITROUS OXIDE TEST: AN IMPROVED METHOD FOR THE DETECTION OF LEFT-TO-RIGHT SHUNTS. <i>Andrew G. Morrow, Richard J. Sanders and Eugene Braunwald</i>	284
CLINICAL PROGRESS	
ANESTHESIA IN PATIENTS WITH HEART DISEASE. <i>Leroy D. Vandam and Thomas K. Burnap</i>	292
ABSTRACTS.....	299
AMERICAN HEART ASSOCIATION.....	315
CONTRIBUTORS TO THIS ISSUE.....	318